ANALYSIS OF PROGRAM ACTIVITIES
NATIONAL INSTITUTES OF HEALTH
1954

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

NATIONAL INSTITUTES OF HEALTH
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NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

Annual Report of Extramural Program activities

Introduction

During the calendar year of 1954, the extramural activities of the National Institute of Neurological Diseases and Blindness continued to expand as shown later in this report. Because of the increased funds provided in the appropriation for fiscal 1955, it has been possible to come somewhat nearer to meeting the needs in research and training in the fields of neurological and sensory disorders. The restoration of Predoctoral Fellowships to the National Institutes of Health has made possible once more the practice of "building from the bottom" which is essential in order to maintain a continuous production of research workers. Increased funds for training grants have provided more needed support of trainees of the National Institute of Neurological Diseases and Blindness. In spite of this increase, the support of the graduate traineeship program is still quite inadequate to award the majority of approved applications from medical schools and universities. In this connection, even though funds of the National Institute of Neurological Diseases and Blindness are not involved, it should be noted that the program of traineeships in Rehabilitation supported by training grant awards from the National Heart Institute, but administered for the past three years by the National Institute of Neurological Diseases and Blindness, will pass to the Office of Vocational Rehabilitation with the close of fiscal 1955.

Program as a Whole

The increasing support by means of research and training grants, fellowships, and traineeships in the fields of interest of the National Institute of Neurological Diseases and Blindness is shown in Table I.

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Table I

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

Number of Projects or Individuals Supported and Amounts of Appropriations under Extramural Programs by Type of Program for Each Fiscal Year

Type of Program	Fiscal Years							
	1952		1953*		1954		1955	
	No.	Amount	No.	Amount	No.	Amount	No. 1/	Amount
Research Grants	119	1,015,000	126	1,326,000	284	2,700,000	296	3,900,000
Training Grants	0	0	6	58,500	23	400,000	33	900,000
Fellowships	15	51,400	43	150,000	32	150,000	20	150,000
Training Stipends	11	36,000	13	51,500	32	104,000	23	104,000
Program Operation	2	20,530	2	22,000	6	48,000	6	58,100

*Available for obligations after comparative transfers
1/ To date, January 1, 1955

From January 1, 1954 through December 31, 1954, 349 research grants have been supported, the total funds involved being $3,540,840. This sum comes partly from fiscal 1954 and partly from fiscal 1955. One hundred and twelve institutions (medical schools, universities, colleges, hospitals, research foundations, etc.) have received this support at an average level of $10,146. In addition, 66 requests for funds were received which the review committees did not feel warranted approval in competition with those projects recommended for support. Thus, the approval rate for this year averaged slightly over 80%.

Table II shows the total number of grants and the sum involved by Disease Categories for fiscal 1954 and fiscal 1955, to date. (The apparent discrepancy between the total figures shown here and in the summary given above is due to the showing of calendar year in the first instance and of fiscal years in the second.)

Table II
RESEARCH GRANT SUPPORT BY CATEGORY OF DISEASE OR DISORDER

Disease Category	No. Grants	1954 Amount	No. Grants	1955[1] Amount
I. NEUROLOGIC DISORDERS				
A. Cerebral Palsy				
1. Cerebral Palsies of Infancy & Childhood	23	$191,903	32	$293,828
2. Parkinsonism & Extrapyramidal Disease	5	84,717	6	62,297
3. Cerebrovascular Disease	18	174,123	21	178,881
4. Cerebellar Disease	1	3,243		
	47	$453,986	59	$535,006
B. Epilepsy & Paroxysmal Disorders	27	282,445	34	536,285
C. Multiple Sclerosis & Demyelinating Diseases				
1. Multiple Sclerosis	3	$ 24,712	4	$ 36,505
2. Amyotrophic Lateral Sclerosis				
3. Subacute Combined Degeneration				
4. Other Demyelinating Diseases	13	216,654	14	197,555
	16	$241,366	18	$234,060
D. Muscular Dystrophy & Neuromuscular Disorders				
1. Muscular Atrophies & Dystrophies	7	$ 66,274	8	$ 75,188
2. Myasthenia Gravis & The Myotonias			1	8,734
3. Collagenous Disorders Affecting the Nervous System				
4. The Neuropathies	16	171,223	18	147,699
	23	$237,497	27	$231,621
E. Injuries to the Nervous System				
1. Traumatic	17	$144,969	24	$160,017
2. Radiation	7	155,894	5	60,162
3. Toxic				
4. Other	3	13,406	5	28,663
	27	$314,269	34	$248,842
F. Infectious Diseases of Nervous System				
1. Poliomyelitis	2	$ 8,356	1	$ 2,057
2. Encephalitis			1	9,341
3. Encephalomyelitis	1	24,663	1	19,669
4. Meningitis				
5. Neuritis (General)			1	4,522
	3	$ 33,019	4	$ 35,589
G. General Metabolic & Deficiency States	34	$368,829	43	$392,825
H. Other Disorders of Nervous System				
1. Vascular Disease (exclusive of cerebrovascular)	10	$102,936	8	$ 74,408
2. Memory, Learning, & Behavior	1	9,158	4	60,382
3. Research of Public Health Significance	1	5,000	1	9,215
	12	$117,094	13	$144,005
TOTALS	189	$2,048,505	232	$2,358,233

1/ To January 1, 1955

Disease Category	No. Grants	1954 Amount	No. Grants	1955 1/ Amount
II. SENSORY DISORDERS				
A. Ophthalmic Disorders				
1. Congenital Malformation	11	$ 52,884	13	$ 58,103
2. Injuries				
a. Traumatic	2	10,920	3	20,341
b. Toxic	1	11,736	1	12,140
	3	$ 22,656	4	$ 32,481
3. Infectious, Inflammatory, etc.				
a. Keratitis			1	$ 18,727
b. Nematode	1	$ 8,788	1	9,000
c. Uveitis	4	35,071	5	48,273
d. General	1	14,000	2	20,480
	6	$57,859	9	$ 96,280
4. Metabolic & Degenerative				
a. Cataract	7	$ 53,095	6	$ 46,471
b. Glaucoma	9	109,264	11	127,156
c. Retinopathy	4	38,898	9	141,503
d. Retrolental Fibroplasia	16	61,490	10	83,061
e. Retinal Detachment	5	48,694	4	44,766
f. Corneal Opacities	2	17,261	1	15,719
g. Senile Blindness	2	22,284	2	24,000
h. General Studies	2	20,061	6	57,106
	47	$371,047	49	$539,782
5. Neuromuscular Eye Disorders				
a. Strabismus	2	3,381	2	9,062
6. Other Ophthalmic Disorders				
a. Hysterical Amblyopia	1	6,316		
7. Research of Public Health Significance	1	11,382		
	71	$525,525	77	$735,708
B. Otologic Disorders				
1. Auditory Impairment	8	$ 78,353	11	$132,900
2. Validation of Hearing Tests	1	7,668	2	15,660
3. Vertigo (Labyrinthine Disease)	1	8,316	3	25,697
	10	$ 94,337	16	174,257
TOTALS	81	$619,862	93	$909,965
III. NEUROSENSORY DISORDERS				
A. Pain	9	$ 89,054	10	$ 93,658
B. Olfaction	2	18,000	4	28,733
C. Tactile	1	9,029	1	8,996
D. General Studies	3	25,772	4	42,621
TOTALS	15	$141,855	19	$174,008
GRAND TOTALS	285	$2,810,222	344	$3,442,206

1/ To January 1, 1955

A study of all of the research grants awarded by the National Institute of Neurological Diseases and Blindness has been undertaken in order to discover trends in the areas and techniques of research in neurological and sensory disorders. In addition, this study will reveal which fundamental disciplines of science are contributing the most to an understanding of these disorders.

During the past year several major advances in research have been made. First, the cooperative grant program to study Retrolental Fibroplasia has yielded sufficient data to enable definite conclusions to be drawn. It has become evident that there is a significant relationship between the concentration of oxygen administered, together with the duration of its administration, and this disease. Still to be determined is under what clinical circumstances should oxygen be used and at what levels and for what durations.

Still another achievement has been made in the evaluation and prevention of kernicterus, a form of cerebral palsy which results from blood incompatibilities involving the Rh factor. An Institute grantee has devised a method for more precisely determining the concentration of bile pigment which can be tolerated in the blood before sufficient brain damage occurs. The development of these new precision methods provide a means whereby physicians now can prevent kernicterus in the majority of instances by administering multiple exchange blood transfusions. These discoveries have led to additional promising projects designed to reveal the fundamental cause of kernicterus.

The discovery that asparagine has apparent beneficial effect in the treatment of certain types of epilepsy has resulted in another controlled cooperative study being undertaken to discover the efficacy of this material. In this instance there is careful integration of five selected extramural research projects with the intramural program of the Institute. It is anticipated that significant findings will be obtained in approximately one year.

Graduate Training Grants

It is only within the past calendar year that the graduate training grants program has become activated on a realistic fiscal basis. Created to help relieve the acute shortage of qualified teachers and clinical research scientists in neurological and ophthalmic disorders, the program is now rapidly gaining momentum. A small number of specialists have been trained and have gone forth to join other groups to set up new training centers. By another year some 30 additional specialists should become available. During the current year, 40 programs in 35 training institutions have been under way; grants to them totaling $740,512.

The Training Grants Committee is developing plans to evaluate the quality of training and productivity of the training programs now receiving support. The committee feels deeply its responsibility to raise the quality of training and to increase the number of trained specialists in this field. The needs continue to be greater than the funds available for this purpose. At the end of this calendar year, 20 requests for funds, totaling $433,679, are awaiting action of the Training Committees, while only $370,000 is still available to support these applications.

It is essential to extend the support of training into the medical sciences related to neurological and sensory disorders in order to increase the fundamental knowledge which can be utilized in the solution of clinical problems in these fields. The training of additional scientists in the fields of biochemistry, physiology, pharmacology, and similar areas would provide scientists for departments of neurology and ophthalmology who could give the student and graduate trainee the necessary breadth of scientific knowledge to make him a more successful clinical worker, ophthalmologist or laboratory research specialist.

In addition, it is proposed to undertake several training grants in the area of teaching of science. New educational techniques and methods of teaching have been developed, and should be applied in the fields of neurology and ophthalmology.

Research Fellowships

The event of most significance to the fellowship program this year was the restoration of the predoctoral awards made possible by a decision of Congress early last year and put into operation on July 1, 1954. It is becoming increasingly imperative to arouse the interest of the student in the very first few years after graduation in order to recruit the manpower for work in this field in competition with the physical sciences, pure and applied chemistry, engineering and other fields.

A consideration of Table III will emphasize this point.

Table III

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS
Number of Research Fellowships and Amount of Funds Awarded
by Fellowship Level and Fiscal Year

Level	1952		1953		1954		1955*	
	Number Awards	Amount Awarded	Number Awards	Amount Awarded	Number Awards	Amount Awarded	Number Awards	Amount Awarded
Pre-doctoral	5	11,912	19	46,285	None	Funds not provided	7	17,165
Post-doctoral	9	32,758	23	95,605	27	114,197	13	52,604
Special	1	3,375	1	6,600	5	35,550	0	0
Totals	15	48,045	43	148,490	32	149,747	20	69,769

*To January 1, 1955

It is evident that this program has not recovered from the effects of eliminating the predoctoral funds during fiscal 1954. There are signs now, however, that the request rate is increasing as those still in research training make plans for the next academic year. Twenty-nine requests are presently at hand awaiting review. These new requests, together with those anticipated before the next year begins, and certain commitments already made will bring the number of fellowship applications approved above the 1953 level. Unfortunately, once again there will be a number of approved fellowships which cannot be awarded because of an insufficiency of funds appropriated for this purpose.

Clinical Traineeships

As a complement to the training grant program previously considered in this report, the Clinical Traineeship program aims to increase the number and quality of academic neurologists, ophthalmologists and allied medical

personnel in the fields related specifically to the neurological and sensory diseases. To accomplish this, clinical traineeships are paid directly to a successful applicant to allow him to seek training wherever he has made the appropriate arrangements to fit his particular case.

The award and financial history of this program is shown in the following table.

Table IV

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS
Number of Clinical Traineeships Approved and Disapproved
and Amounts of Approved Funds Involved
by Traineeship Field and Fiscal Year

	Field	1952		1953		1954		1955*	
		No.	Amount	No.	Amount	No.	Amount	No.	Amount
Awarded	Neurology	4	13,800	5	12,244	21	68,885	12	39,416
	Ophthalmology	0	0	0	0	2	7,200	8	27,600
	Rehabilitation	7	17,322	8	22,425	9	24,900	3	9,400
	Totals	11	31,122	13	34,669	32	100,985	23	76,416
Approved but Unpaid	Neurology	0	0	0	0	7	23,400	14	47,400
	Ophthalmology	0	0	0	0	0	0	5	16,800
	Rehabilitation	8	19,000	17	43,400	2	5,200	5	12,200
	Totals	8	19,000	17	43,400	9	28,600	24	76,400
Disapproved	Neurology	0	0	0	0	0	0	1	0
	Ophthalmology	0	0	0	0	0	0	0	0
	Rehabilitation	1	0	1	0	2	0	0	0
	Totals	1	0	1	0	2	0	1	0

*To January 1, 1955

Reference to Table IV shows conclusively that the traineeship portion of the Intramural Program is the least adequately supported. In each of the three major divisions, i.e.; neurology, ophthalmology, and rehabilitation; it has not been possible to award traineeships to more than one-half of the scientifically approved applications. It is essential to the success of this program that additional funds be provided for traineeships.

Program Operation

In this fourth year of operation of the Extramural Program of the National Institute of Neurological Diseases and Blindness, during which the funds for grants have increased four-fold, the operating costs have increased less than three-fold as compared with the first year of operation.

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES & BLINDNESS

PROGRAM ANALYSIS

The National Institute of Neurological Diseases & Blindness has a very broad objective, namely; the development of means for the prevention, diagnosis, and treatment of neurological and sensory disorders which include some 200 disease entities and which affect approximately 20 million persons in the United States today.

The major effort is directed toward those chronic diseases and conditions which are severely disabling to the largest number of people over long periods of time. Among the more important of these are cerebral palsy, epilepsy, multiple sclerosis, muscular dystrophy, cerebral vascular disease, the blinding diseases, and diseases affecting the other special senses. In most of these diseases the manifestations are multiple and complex, and the etiology is obscure or little understood. In addition, the essential facts underlying the physiology and chemistry of the nervous system are unknown. This requires a fundamental as well as a clinical approach to the causes of these diseases.

In order to accomplish these objectives, three major programs of research have been initiated. These are: (1) an intramural program of clinical and laboratory research on specific neurological and sensory disorders of unknown etiology, together with practical approaches to medication and surgery for their alleviation; (2) an intramural fundamental research program on the structure, biochemistry,

and physiology of the nerve cells and fibres, the nutrition and metabolism of nervous tissue and the brain, and the sensori-motor functions of the nervous system; and an extramural program which provides a broad attack on the entire field of neurology and blindness with research grants for clinical and fundamental studies, with training grants for providing more and better training of medical and research personnel, and with fellowships and traineeships for attracting new scientists to the field or increasing the competence of those already in the field.

These three major programs of research are well integrated and coordinated. The laboratory and clinical aspects of the intramural program are reviewed in conferences and seminars in order to provide early application of research findings in clinical cases and to avoid duplication of effort. In areas of research where a broad, scientific attack upon a baffling disease is essential, collaborative projects are established. Scientists working under the extramural research grant program of the Institute cooperate with the intramural laboratory and clinical staff in a multidisciplinary approach to the problem under the guidance of a panel of experts from various scientific fields. Thus, without overlap, and with a comprehensive and united approach, the reservoirs of scientific knowledge and technical skills are brought to bear upon an important problem in an incomparable manner.

The program of the National Institute of Neurological Diseases and Blindness for 1956, which reflects the above approach to problems in these areas, is analyzed as follows:

Amount of Support

I. Intramural Research $2,329,000

A. Laboratory Investigations 654,150

An intelligent attack upon the problems of the neurological and sensory disorders, as in the study of other diseases, must consist not only of an intensive study of the disease as it exists in patients, but also of a comprehensive foundation of basic research upon the structure, development, and function of the normal nervous system. Only by understanding the normal is it possible to diagnose and explain the abnormal, to delineate what factors must be corrected by therapy, to determine rational treatment and prevention, and to predict the results. The importance of basic research is especially apparent in the case of the nervous system, which is, by far, the most complex entity in the body, and the least understood. It is well recognized that significant advances in neurological and sensory disorders are possible only through greater knowledge provided by laboratories in which the techniques of physics and chemistry are applied effectively in the disciplines of physiology, biochemistry, pharmacology, and organic and biophysical chemistry.

1. Neurologic Disorders $607,150

a. Cerebral palsy and chronic cerebral disorders ($145,000) - laboratory studies of the embryology, anatomy, pathology, cytology, and biochemistry of the nerve cells and fibres of the brain and spinal cord, including experimental production of cerebral palsy in animals by means of anoxia, birth injury, anesthetics, and vascular cerebral damage.

b. Epilepsy and other paroxysmal cerebral disorders (0) - laboratory studies of the biochemistry and pharmacology of convulsive disorders.

Amount of Support

c. Multiple sclerosis and demyelinating diseases ($160,000) - laboratory studies of the microstructure of nerve cells, fibres, junctions, and terminals, utilizing the electron microscope; basic biochemistry and micro-biochemistry of the central nervous system, especially relating to the myelin or protective covering of nerve fibres; and electrophysiological studies of the nerve impulse.

d. Muscular dystrophy and neuromuscular disorders ($177,000) - utilization of physical and chemical techniques in the measurement and interpretation of rapid ion movements within the individual nerve cell and in the studies of permeability of nerve membranes, energy transfer, including the effects of drugs on the enzymatic activity of nerve cells.

e. General metabolic and deficiency disorders of the nervous system ($13,150) - experimental studies of the thermo-regulatory mechanisms of the autonomic nervous system and the effects of various drugs on the heat-regulating centers in the brain.

f. Poliomyelitis and other infectious diseases of the nervous system (0) - no active projects.

g. Accident and injury to the nervous system ($103,000) - experimental investigations of regeneration in the central nervous system, including studies of fever-producing mechanisms facilitating the regeneration and the effects of end-organs on the induction of neuronal specificity.

h. Other disorders of the nervous system not included above ($9,000) - electrophysiological studies of nervous transmission and central excitatory state of the spinal cord.

Amount of Support

2. Sensory Disorders $47,000

a. Disorders of hearing and balance ($14,500) - neuro-anatomical studies of the auditory and vestibular tracts, including electrophysiological investigations of the function of newly discovered efferent fibers within the afferent bundles, as well as studies of the sensory mechanism of the inner ear.

b. Disorders of vision ($18,500)
(1) - (7) - no active projects

(8) Other ophthalmic disorders, including injuries ($18,500) neuro-anatomical, neurophysiological, and electrophysiological investigations of the visual apparatus, including the sensory cells, optic tracts and cortical connections.

c. Disorders of the other special senses (taste, smell, touch, and pain) ($14,000) - histochemical studies of the effects of anesthetic agents on the central nervous system in the alleviation of pain, including toxic, pathologic, and fatal damage.

B. Clinical Investigations $1,674,850

The Clinical Investigative Unit of the National Institute of Neurological Diseases and Blindness has several major objectives in the study of neurological and sensory disorders. The main objective of this Unit is to apply basic techniques utilizing biochemical, biophysical, electronic, and pathological advances to the study of neuromuscular diseases. This will include (1) the clinical study of in - and outpatients;

(2) the analysis of biochemical changes that occur in the central and peripheral nervous system and in muscle tissue; (3) the clinical testing of pharmaceuticals used in the treatment of such diseases; (4) the development and evaluation of surgical and other physical means of diagnosis and treatment; and (5) epidemiological studies. The study of the clinical manifestations of disease in the patient and the correlation of these findings with neurological, biochemical, and pathological data is the only practical method of implementing the discoveries of the basic sciences. The research program of this Unit is described as follows:

1. Neurologic Disorders $1,223,800

   a. Cerebral palsy and chronic cerebral disorders ($178,000) - to study the clinicopathologic findings and malformations of the nervous system occurring in patients with cerebral palsy and other chronic diseases of the cerebrum and cerebellum.

   b. Epilepsy and other paroxysmal cerebral disorders ($820,000) - to study the chemistry, electrophysiology, electrical brain wave patterns, psychology, and pathology of paroxysmal cerebral disorders as well as surgical and pharmacological techniques for the alleviation or reduction of such seizures.

   c. Multiple sclerosis and demyelinating diseases ($32,400) - studies of the etiology, clinical manifestations, pathology, and epidemiology of demyelinating diseases; to continue the chemical and electrophoretic analyses of cerebrospinal fluid in patients suffering from multiple sclerosis; the etiology and pathogenesis of encephalomyelitis; and the evaluation of iso-nicotinic acid hydrazide as a therapeutic agent.

Amount of Support

d. Muscular dystrophy and neuromuscular disease ($149,000) - to study the biochemistry and ion exchange of muscle tissues in normal subjects and in patients with neuromuscular disease, and to continue work on electrical recording of muscular responses in patients with myasthenia gravis and other neuromuscular diseases.

e. General metabolic and deficiency disorders of the nervous system ($8,900) - studies of the biochemistry, physiology, and pharmacology of the nervous system.

f. Poliomyelitis and other infectious diseases of the nervous system ($15,800) - studies of relationships between blood and spinal fluid glucose in the mechanisms and treatment of meningitis and other infectious diseases.

g. Accident and injury to the nervous system ($10,800) - studies of fever producing and similar substances in the regeneration of central nervous tissue, and studies of the fever mechanisms which are of great importance as causative agents of many destructive processes of the central nervous system.

h. Other disorders of the nervous system not included above ($8,900) - studies of the neuro-anatomical and neurophysiological aspects of nervous diseases.

2. Sensory Disorders $451,050

a. Disorders of hearing and balance ($10,800) - studies of the effect of removal of one temporal lobe on the hearing of patients who develop a receptive type of asphasic disorder, as well as the effect upon vision and vestibular reflexes important for posture and the maintenance of balance.

b. Disorders of vision - ($425,500)
(1) Cataract ($58,300) - to continue studies on the metabolic and

Amount of Support

physical etiological factors in the formation of cataracts.

(2) Glaucoma ($46,700) - to conduct tonographic studies of intraocular pressure in cases of acute and chronic glaucoma.

(3) Retinopathy ($18,300) - to study the electrical response of the human retina in various pathological conditions of the eye, especially retinopathy.

(4) Retrolental fibroplasia (0) - to investigate the etiology of this blinding disease and to determine the mechanism by which oxygen given to premature babies precipitates the condition.

(5) Uveitis, keratitis, and other inflammatory and parasitic diseases ($190,000) to conduct studies in posterior granulomatous uveitis and its relation to toxoplasmosis and to virus infections and to investigate other inflammatory diseases of the eye, as well as to develop and evaluate therapeutic measures.

(6) Metabolic and degenerative diseases of the eye ($38,200) - to evaluate the use of l-asparagine in the treatment of retinitis pigmentosa.

(7) Strabismus and neuromuscular disorders ($31,500) - to conduct studies on the diagnosis and treatment of neuromuscular anomalies of the eyes, and to evaluate various diagnostic and therapeutic devices and techniques.

Amount of Support

(8) Other ophthalmic disorders, including injuries ($42,500) to study lesions of the optic pathways in the brain and neoplasms of the eye and orbit; and to develop new instruments and devices for testing eyes.

c. Disorders of the other special senses (taste, smell, touch, and pain) ($14,750) - studies of surgical techniques and various blocking agents in the relief of intractable pain.

II. Extramural Grants Program $5,054,000

The Extramural Grants Program of the National Institute of Neurological Diseases & Blindness has three major objectives in contributing to the mission of this Institute in the understanding and treatment of neurological and sensory disorders. These are, first, a very broad fundamental study of these disorders by means of research grants supporting work on the anatomy, embryology, neurology, physiology, biochemistry, and histology of the brain and central nervous systems of man and the lower animals. In addition, clinical and pathological studies, along with surgical, pharmacological and other techniques for diagnosis and treatment, are supported. Second, training grants are awarded to selected university and medical centers in order to help alleviate the present critical shortage of qualified personnel in the fundamental sciences related to neurological diseases and blindness, which are needed to do the research required to advance the frontier of medical science in these areas. Finally, in order to attract more young men to these neglected fields, and to improve the competence of those already in these or related fields, pre-doctoral, post-doctoral, and special fellowships are awarded to exceptional men who have demonstrated special interest and who show unusual promise for development as research workers or teachers in neurology and opnthalmology. In addition, clinical traineeships are awarded to neurologists, ophthalmologists, and paramedical personnel in fields related to neurology and sensory diseases.

Amount of Support

A. Research Grants $3,900,000

1. Neurologic Disorders $2,672,500

a. Cerebral palsy and chronic cerebral disorders ($606,000) - laboratory and clinical studies of the anatomical, physiological, biochemical, pharmacological, and pathological factors important in the etiology, clinical manifestations, and pathologic findings in cerebral palsy and other chronic diseases of the cerebrum and cerebellum.

b. Epilepsy and other paroxysmal cerebral disorders ($608,000) - laboratory and clinical studies of paroxysmal cerebral disorders including biochemical, physiological, and electrophysiological analyses of the brain and nervous tissue.

c. Multiple sclerosis and demyelinating diseases ($265,000) - biochemical and metabolic studies of nerve and brain tissues in the demyelinating diseases, and the investigation of the immunologic mechanism of these diseases.

d. Muscular dystrophy and neuromuscular disease ($262,000) - studies of the cytology, physiology, and biochemistry of nerve and muscle and their junctions; the effects of diet, metabolism, and hormones on nervous transmission; electrophysiological studies of nerve-muscle action; nerve regeneration, chemotherapy, and pharmacology of the peripheral nervous system.

e. General metabolic and deficiency disorders of the nervous system ($445,000) - studies of the nutrition, etabolism, and electrophysiology of the brain and nervous system; the effects of endocrines and pharmaceuticals on the biochemistry and function of the central nervous system, and the pharmacology of anesthetics and analgesics.

Amount of Support

f. Poliomyelitis and other infectious diseases of the nervous system ($40,500) - neurophysiological and clinical studies of virus and other infectious diseases, including studies of respiration, circulation, and muscular atrophy in cases of poliomyelitis.

g. Accident and injury to the nervous system ($283,000) - neuroanatomical, embryological, biochemical, neurophysiological, and pathological studies of the brain and spinal cord in cases of traumatic, vascular, and radiological insult to the central nervous system, including investigations of nerve degeneration and regeneration, as well as studies of the metabolism and autonomic function of paraplegics.

h. Other disorders of the nervous system not included above ($163,000) - laboratory and clinical research on neuroanatomy, experimental embryology, biochemistry, physiology, and pharmacology of the brain, central and autonomic nervous systems.

2. Sensory Disorders $1,227,500

a. Disorders of hearing and balance ($197,500) - embryological, physiological, biochemical, neurological, pathological and psychological studies of the senses of hearing and balance, including tests of hearing.

b. Disorders of Vision ($832,500)

(1) Cataract ($52,500) - studies of the embryology, physiology, biochemistry, and metabolism of the eye as related to the formation of cataracts.

Amount of Support

(2) Glaucoma ($144,000) - studies of the biochemical, metabolic, and circulatory factors in the secretion and elimination of intraocular fluids, and the measurement of intraocular pressure when this system is disturbed by diseases or other processes.

(3) Retinopathy ($160,000) - studies of non-inflammatory diseases of the retina of the human eye, especially as affected by circulatory and metabolic disturbances, including the pathogenesis and therapeutics of these conditions.

(4) Retrolental Fibroplasia ($94,000) - to investigate the etiology of this blinding disease in infants, and to determine the mechanism by which oxygen given to premature babies precipitates this condition.

(5) Uveitis, keratitis, and other inflammatory and parasitic diseases ($109,000) - etiological, clinical, and therapeutic studies of virus and parasitic diseases which produce serious inflammatory conditions of the eyes, often resulting in blindness.

(6) Metabolic and degenerative diseases of the eye ($226,000) - neuropathological and histological studies of degenerative processes in the human eye, including those changes related to advanced age.

(7) Strabismus and neuromuscular disorders ($10,000) - studies of the effects of loss of vision on the development of muscular anomalies of the eyes, including recording of electrical activity in the brain of patients with such disorders.

Amount of Support

(8) Other ophthalmic disorders, including injuries ($37,000) - anomalies of embryological and neurological development of the eyes, biochemical studies of the light sensitive structures, and ocular tumors as well as traumatic conditions.

c. Disorders of the other special senses (taste, smell, touch, and pain) ($197,500) - neurophysiological and sensory studies of the other special senses, including extensive investigations of pain and the effectiveness of analgesics, anesthetics, and nerve blocking in providing relief from intractable pain.

B. Training and Development of Scientists in the Fields of Neurological Diseases and Sensory Disorders — $1,154,000

The major cause of lack of significant progress in the diagnosis and treatment of neurological and sensory disorders is the shortage of scientifically trained personnel in neurology, pathology, sensory physiology, and the allied fundamental sciences. It is essential, therefore, to train clinical teachers and research workers in these fields and, in many cases, to provide training facilities. The latter is necessary because prior to 1954 less than one-third of all of the medical schools in the United States had complete neurological units for teaching physicians and scientists; many teachers of neurology were not qualified neurologists; and in several States there was not a single qualified neurologist. Similarly, about one-fourth as many ophthalmologists are being trained as are needed. Grants are made to teaching institutions and to individuals to aid in filling this tremendous gap in important scientific fields.

a. Training Grants ($900,000) - are awarded to teaching institutions to begin or increase their training programs in all fields related to neurological and sensory disorders in order to reduce the critical shortage of clinical teachers and investigators.

Amount of Support

b. Research fellowships ($150,000) - are awarded to individuals at both the predoctoral and postdoctoral level, and special research fellowships are awarded to distinguished scientists, in order to permit them to devote full-time to increasing their competence in research in the fields of neurological and sensory disorders and related disciplines.

c. Training stipends ($104,000) - are awarded to medical doctors in all branches of medicine in order to provide them with special training in the diagnosis, treatment, and care of patients with neurological and sensory disorders.

GRAND TOTAL $7,383,000*

* All of the above figures for direct operations include pro-rata share for central services provided by the National Institutes of Health. In addition to the grand total of support shown above, the 1954 appropriation of $7,600,500 includes $217,500 for such items as program direction and administration, National Advisory Council for Neurological Diseases and Blindness, certain consultant groups, administration of research and training grants, and publications and reports.

ANNUAL REPORT OF THE BASIC RESEARCH PROGRAM, NIMH-NINDB

JANUARY 1 TO DECEMBER 31, 1954

Seymour S. Kety, Scientific Director

The human nervous system constitutes the most complicated yet most beautifully designed instrument in the universe and, despite the gratifying strides which have been made toward understanding its functions and disorders, our ignorance here remains great and challenging. This ignorance is demonstrated by the fact that mental and nervous disease still constitute the greatest cause for disability in all the countries of the world, including our own. Research in these areas must encompass careful, critical studies of these diseases as they occur in patients, but, equally important, it must also include those fundamental studies designed to increase our knowledge of the structure and function of the nervous system in health and in disease. It is for this reason that the two Institutes at the National Institutes of Health primarily concerned with mental and neurological diseases have pooled their resources for basic research into a single combined program. Since it is difficult, if not impossible, to predict from which basic research areas will come information of greatest practical diagnostic or therapeutic value, a well-balanced program must include representative research in all of the major areas. Such a program also makes assured the most fruitful collaboration and exchange of information between disciplines for the mental and neurological diseases do not confine themselves rigidly to the nervous system alone or to only one aspect of its function, and the great contributions to medicine in the past have usually arisen as a result of the utilization of knowledge acquired by many investigators in many different fields. By drawing together outstanding representatives of all of the relevant sciences, any new finding in one laboratory can be subjected to critical analysis by all of the other disciplines and immediate exploitation of its ramifications throughout as many different fields as possible.

By the end of year 1954, this purpose had been realized for the Basic Research Program of NIMH and NINDB. This program now has eight Laboratories, and a total staff of 55 professional and 70 supporting personnel actively at work over a broad spectrum which ranges from neuroanatomy, physiology, and biochemistry through the psychological and sociological fields. The completion of the laboratory space in the Clinical Center allocated to the Basic Research Program occurred in the latter part of 1954, permitting the establishment of two new laboratories. The program was fortunate in the appointment of two outstanding scientists as laboratory chiefs: To the Laboratory of Cellular Pharmacology, Dr. Giulio L. Cantoni, well-known for his discovery of active methionine, responsible for many of the biochemical transformations which take place in the organism, and Dr. Kenneth S. Cole to the Laboratory of Biophysics, a scientist whose classical studies of the electrical properties of conducting nerves laid the groundwork for the most important contributions to neural transmission which have thus far been made. The Laboratories of Neuroanatomical Sciences, Neurophysiology, Neurochemistry, Psychology, and Socio-environmental Studies, and the Addiction Research Center at Lexington, Kentucky, established in previous years have completed their organization and continued productive activity.

The research of the various laboratories for the past year and their plans for the future can best be described in terms of certain important areas of knowledge including structure, function, and metabolism of the nervous system, the biochemical basis of therapy, the study of drug addiction, the development, regeneration and aging of the nervous system, perception and behavior, and human relations.

THE STRUCTURE OF THE NERVOUS SYSTEM

Unlike many organs which are homogeneous in structure and perform well-defined functions, the brain is a baffling collection of thousands of individual components controlling many different functions and communicating with each other by a magnificently developed network of fibers and pathways. Many of these pathways are still obscure and a primary function of the Laboratory of Neuroanatomy under Dr. William Windle is to find the order and the organization of the nervous system. In the past year, Dr. Rasmussen, well-known for his previous discoveries of important new fiber tracts, has been tracing the little understood frontopontine tract (NINDB L-31) in man, a pathway which goes from the frontal part of the brain to important areas in the brain stem and which is one of the fiber tracts which is cut in the operation of frontal lobotomy. His studies have also included the tracing of fibers from the brain into the spinal cord, knowledge of which is almost completely lacking and yet important to our understanding of coordinated motor activity and spastic states (NINDB L-30). Dr. Rasmussen is also continuing studies of pathways involved in hearing (NINDB L-28 and L-29). Anatomical and physiological research has long been plagued by the lack of a technique for demonstrating the precise termination of nerve fibers within the brain and spinal cord. Further perfection of a technique developed elsewhere by Nauta has made available a method which appears to be adequate for the determination of the precise endings in the central nervous system of the minute ramifications of nerve fibers (NINDB L-30). This has opened a door long closed to investigators in neurology.

The physical and anatomical properties of the spinal cord and its coverings having to do with the support of blood flow to and from this organ and playing a role in the prevention of edema under certain adverse circumstances are being studied in comparative anatomical and physiological experiments (NINDB L-12 and L-22).

Although classical neuroanatomy was dependent upon empirical examination of nervous tissue stained by various dyes, newer techniques have in recent years placed in the hands of scientists cytochemical methods for the study of structure which are infinitely more precise, more exact and more closely related to function and metabolism. These techniques permit the detailed chemical analysis of individual cells in the nervous system either by specific chemical stains or by actual microchemical analysis of single neurones. Alert to these new possibilities, the Laboratory of Neuroanatomical Sciences has established a Section on Neurocytology where Drs. Albers and Guth are developing and perfecting their tools for this research (NINDB L-17, L-18 and L-19). Studies employing some of these techniques are being applied

to the effects of anesthetics upon the cells of various parts of the nervous system (NINDB L-21) and the distribution of gamma-aminobutyric acid, a substance found only in the central nervous system (NINDB L-16). Dr. Cammermeyer, Visiting Scientist in Experimental Neuropathology, is investigating the structure and reactions of the area postrema (NINDB L-24) in a number of different species in an effort to define the nature and function of this structure which seems to be intimately concerned with the nutrition of the brain, the production of cerebrospinal fluid, and may even have a still unprobed function in the production of hormones. With the pending appointment of an outstanding specialist in the application of electron-microscopy to the nervous system (NINDB L-13), this important tool to studies of the structure of the nervous system will be added.

FUNCTION OF THE NERVOUS SYSTEM

The essential function of the nervous system is to receive, evaluate, and store information from the outside world and to use this information in determining present and future behavior in such a way as to achieve coordinated, purposeful and useful activity. It is well established that in order to perform this function, the nervous system operates in a manner similar to that of a beautifully organized communication network, like such a network, employing electrical messages, and utilizing ingenious components of which man-made transmitters, receivers, amplifiers and relays are merely the crudest counterparts. To investigate the functional or physiological phenomena which occur in the nervous system and which mediate behavior, the combined research program has established two laboratories, one in biophysics and the other in neurophysiology, organized to explore most of the ramifications of this vast field from the properties of single microscopic components to the characteristics of organized activity at the very highest levels.

Neural Transmission. Of fundamental importance is the nature of the electrical impulse itself which mediates the activity of the nervous system by its transmission along the nerve fiber. A number of projects of these two laboratories have been established to study various aspects of the nerve impulse in an effort to determine how it originates and the factors which modify it, normally and through the influence of drugs and disease. Dr. K. S. Cole, some fifteen years ago, reported studies on the instantaneous conductivity of the nerve fiber during activity which formed the basis of the present concept of the origin of the nerve impulse. This concept attributes the action potential of the nerve to the differential migrations of the charged ions, sodium and potassium, across the nerve membrane. Since this action potential passes any single point in a matter of a few thousandths of a second, these ionic movements must be rapid enough and of sufficient magnitude to account for the changes. The present work of Dr. Cole and his staff (NINDB L-45, L-46, and L-47) is a further development of this theory and its testing by appropriately designed experiments. From the laws of diffusion, coupled with our knowledge of the structure of the nerve fiber and of the properties of the ions involved, it is possible to set up a complex mathematical theory which can predict the formation and behavior of

the nerve impulse under a variety of experimental and pathological conditions. The equations involved are sufficiently complex as to tax the most advanced mathematical concepts and only the recent development of elaborate electronic computers has made practical some of the solutions. Once the fundamental equations are set up, they may be varied by the substitution in them of appropriate factors corresponding to changes in the physiological and pathological states, the solutions then yielding a prediction of what the actual behavior would be. These predictions are then tested against actual experiment using a simple nerve fiber, the giant axon of the squid, as a model. In this way, the theory upon which the mathematical equations are based can be validated. Such comparisons, though limited, have been so satisfactory as to encourage the assumption that these ionic movements and the mechanisms by which they are controlled are a fundamental component of normal and pathological nervous processes. Such findings raise other and equally interesting questions. The fundamental question to be resolved and one which occupies the interest of many outstanding scientists throughout the world is the manner by which the nerve cell, utilizing energy received from the oxidation of foodstuff, can so direct the movements of sodium and potassium as to create the electrical energy needed in its transmission of impulses. Dr. Rich of the Section on Physical Chemistry (NIMH-9) has developed an ingenious theory to account for this process applying information on coupled diffusion, well-known in the field of physical chemistry, to the problem of movement of sodium ions against a diffusion gradient. His group is now in the initial stages of testing this theory. Dr. Tasaki, well-known for his previous contributions to sensory and axon physiology, with his staff at these Institutes has tackled other phases of the problem of nerve transmission. In the past year (NINDB L-36) by means of interesting new techniques which they have developed, an action potential of 100 millivolts was demonstrated to play a decisive role in the initiation and propagation of the impulse in peripheral nerve. They have further described the physical and electrical properties of the nerve fiber and made measurements during the passage of the nerve impulse which are more accurate and less damaging than those of previous workers. These studies will be continued and expanded in the coming year (NINDB L-39 and L-40).

Neuronal Interactions. Next in the level of complexity above the impulse in the nerve fiber is the important question of how nerve cells interact and communicate with each other. Clarification of this single problem would constitute a real landmark in the study of nervous function. Dr. Frank, Chief of the Section on the Spinal Cord, often in collaboration with Dr. Fourtes of the Army Medical Center has addressed himself to this question (NINDB L-32, L-33, and L-34). By means of electrodes so fine that they can be inserted into single cells with a minimal amount of injury and by amplifiers of sufficient sensitivity, the electrical output of single nerve cells in the spinal cord can be recorded. Among the findings of this group are the discovery of certain cells in the spinal cord which respond to a wide variety of peripheral stimuli and which these workers have called "alerting cells" because of the possibility that they serve such a function in the normal animal alerting the spinal motor system of the organism to further purposeful behavior. These workers have found other cells in the spinal cord which are capable of responding to peripheral stimuli with frequency modulated trains

of impulses, suggesting that such modulation conveys information regarding the source of the stimulus. Dr. Frank's report, at a recent meeting of neurophysiologists, of the finding of certain "pacemaker cells" capable of initiating their own characteristic rhythms (NINDB L-33) was generally regarded as one of the most significant contributions reported.

The Hypothalamus. This collection of nuclei lying at the base of the brain and just above the pituitary plays an important role in the regulation of many of the bodily functions including temperature, certain aspects of metabolism, and many of the vegetative functions of the circulation. Recently, the hypothalamus has emerged as the important link between the nervous system on one hand and the endocrine glands on the other by the control which it exercises over the master gland of the body — the pituitary. The hypothalamus also appears to be involved with certain emotional states in a way which is not yet clear so that its implications in psychiatry and clinical medicine are readily seen. Dr. Brightman, recently appointed to the Laboratory of the Neuroanatomical Sciences, is investigating the relationships between the hypothalamus and certain endocrine functions (NINDB L-10 and L-11). By means of special staining technique, the neurosecretory content of the hypothalamus and parts of the pituitary under special conditions can be evaluated and shown to be altered by changes in environmental conditions. His studies to date have shown a relationship between neurosecretory material in the mother and the advent of suckling and milk ejection. These experiments will be expanded to observations upon other important members of the endocrine system to explore these neurohumoral relationships. Another important function of the hypothalamus is the regulation of temperature and body metabolism. A recently appointed investigator to the same laboratory, Dr. Massopust, is investigating the mechanisms of temperature control in the hypothalamus (NINDB L-25) and elsewhere (NINDB L-26) and the action of certain agents which alter temperature (NINDB L-27). His studies to date have localized certain areas of the hypothalamus in which temperature control appear to be confined and altered accepted concepts of the pathways by which temperature regulation is modulated through the spinal cord. Incidental findings have fortified knowledge of the other roles of the hypothalamus in metabolism, emotional states, and the sexual cycle. The use of hypothermia in modern cardiac surgery lends added significance to studies upon the control of temperature.

The Cerebral Cortex. In this, the outer gray layer of the brain, have been thought to reside the highest functions of perception, learning, and judgment. Speculative as this may be, there is little doubt that the cerebral cortex represents a most highly developed and organized portion of the central nervous system. Two groups of investigators have concerned themselves primarily with different aspects of the function of this structure. Dr. Marshall, Chief of the Laboratory of Neurophysiology, who before his appointment to NIH had laid the groundwork of our present knowledge of the sensory functions of the cerebral cortex, has more recently devoted considerable attention to the subarachnoid space (NIMH-2), the collection of delicate membranes and cerebrospinal fluid which overlies the cortex. By improved methods of measuring the oxygen tension and directional blood flow in the cortex, he has studied the effects of the blood-brain barrier on the action

of certain drugs. Other members of this section have measured the electrical resistance of the cerebral cortex (NIMH-5) applying to it techniques similar to those which have earlier been used in peripheral nerve. Dr. Freygang has recently succeeded in recording the electrical activity of single cells of the cerebral cortex as part of an investigation of this activity and the effects upon it of intracellularly applied currents (NIMH-6).

Dr. John Lilly, who was appointed Chief of the Section on Cortical Integration in the Laboratory of Neurophysiology because of his original contributions in that field, has continued his research on the spatial and temporal patterns of electrical activity on the surface of the cortex. By means of a closely packed array of 25 electrodes recording simultaneously, the electrical activity on the surface of the conscious brain is amplified and displayed so as to preserve its spatial and temporal patterns (NIMH-7). In the past year a type of electrical waveform has been developed which does not injure the cells of the brain. This incidental development is a significant practical tool for the neurophysiologist, the neurosurgeon, and others who require a safe and convenient technique for examining and stimulating the human brain in diagnosis and therapy.

Plans for the next year include an initiation and expansion of studies in the functional relationship of the reticular formation of the brain stem, that area recently demonstrated to be an important crossroads for ascending and descending impulses and capable of playing an important role in the coordination of motor activity, the control of the autonomic system, and in sleep, coma, and emotional states.

The Special Senses. At least three investigators in the Basic Research Program, Dr. Marshall, Dr. Tasaki, and Dr. Rasmussen, have in the past made significant contributions to our understanding of vision and hearing. In the past year they have continued their interest in these important fields in a number of specific research projects. Dr. Rasmussen, some years ago, made the new and startling discovery that the auditory nerve, formerly thought to be a pure sensory nerve, contained fibers which conducted impulses from the auditory areas of the cerebral cortex to the cochlea or organ of hearing. This system evidently represents an auditory "feedback" mechanism whose function is still obscure and which he is continuing to investigate (NINDB L-28). He is also studying the autonomic innervation of the inner ear which is generally assumed to play an important role in the proper functioning of the hearing and equilibratory organs. Disturbance in this supply is thought by many otologists to be responsible for a number of disorders such as Meniere's Disease (NINDB L-29).

Although much is known of the anatomy and physiology of various sense organs, no answer is available to the important question of how a particular receptor converts the signals which it receives from the external world into the coded electrical messages which it transmits to the brain. Dr. Tasaki of the Section on Special Senses of the Laboratory of Neurophysiology is continuing his intricate and significant studies in this area (NINDB L-37).

He has also begun a study of the corresponding question in the visual system with the development of techniques and equipment for recording the electrical responses of individual sensory elements in the retina in response to various light stimuli, a study which is expected to shed some light upon the mechanism of color vision and visual physiology in general (NINDB L-38). Dr. Marshall, whose earlier work is regarded as a landmark in visual physiology, has continued his studies of the functional activity of the lateral geniculate nucleus, the important relay station where visual impulses can interact with themselves and with other impulses before passing on to the appropriate areas of the cortex (NIMH-3). These studies became even more interesting in the past year when Dr. Evarts, working with Dr. Marshall, found that an important site of action of the hallucinogenic drug, LSD, was in this visual nucleus. The effects of this same drug on visual function in man are being investigated by Dr. Carlson and Dr. Evarts in the Section on Perception and Learning of the Laboratory of Psychology (NIMH-38-C), where measurable effects upon dark adaptation have already been demonstrated. This section is also developing an ingenious technique for recording eye movements electrically which promises to be a valuable tool in studies of visual perception (NIMH-40). Much of the activity of this section revolves around studies of visual discrimination and perception in animals and man (NIMH-39, 41, and 42).

THE METABOLISM OF THE NERVOUS SYSTEM

The Basic Research Program has secured a wide distribution of competence and interest throughout the important field of the biochemistry of the nervous system from the most basic levels of cellular chemical structure and metabolism through the peculiar biochemical processes of nervous tissue to the nutrition and metabolism of the living brain in health and disease.

The Section on Physical Chemistry under Dr. Rich has chosen as its focus the elucidation of the chemical structure of certain cellular components of fundamental importance. By means of the modern technique of X-ray diffraction measurement (NIMH-13) coupled with standard biochemical methods (NIMH-12, 14, and 15), investigations are under way on the structure, properties, and synthesis of ribonucleic acid, the large molecule within the cell which is believed to be the template upon which the cell constructs the highly specific and complex protein molecules vital, in the nervous system, to the structure, growth, and specific metabolism of the nerve cell. The electron microscope has recently yielded evidence that ribonucleic acid bodies are concentrated at the junctions between nerve cells where lie the integrative and possibly the retentive powers of the nervous system. Other substances, notably those incorporating a heavy metal in a complex organic molecule are being investigated by Dr. Dunitz, Visiting Scientist from Oxford (NIMH-10 and 11). Such compounds are of great significance in biology and include hemoglobin and cytochrome, necessary for oxygen transfer to the neurone, insulin, vitamin B_{12}, and numerous enzyme complexes vital to metabolism. At least one disease of the nervous system (Wilson's Disease) has been shown to be related to an abnormality of copper metabolism in the brain, while the effects of lead and other metallic poisoning are undoubtedly related to lead-complex formation in

the cell. Such complexes with sodium or potassium may lie at the root of the generation of the electrical energy of the nervous system, although one new project of this section (NIMH-9) proposes to test an ingenious and original theory in an attempt to discover the source of this energy.

The Section on Lipid Metabolism under Dr. Brady, who previously made a significant contribution to knowledge of fatty acid synthesis, has concerned itself with the metabolic processes by which the lipids, which constitute a large and still mysterious fraction of brain substance, are formed, converted, and utilized. Research begun in collaboration with Dr. Stadtman of the Heart Institute has demonstrated the presence of new enzymes in brain and other tissues important in the synthesis of energy-rich sulfur compounds which are probably related, in turn, to certain syntheses necessary to nervous function: fatty acids, cholesterol, and acetylcholine (NINDB L-42). Investigation is continuing in order to define the mechanism of utilization of ribose, a 5 carbon sugar, previously demonstrated by members of the section and offering an alternative source of energy and a possible building block for brain lipids (NINDB L-41). Recent demonstration of the excretion of ribose in patients with muscular dystrophy (NINDB-19-C) gives added significance to this study. A major activity of the section lies in the study of acetyl coenzyme A, a complex and recently discovered substance which stands at the crossroads of many metabolic and synthetic processes. It represents the probable pathway by which carbohydrates, fats, and proteins are oxidized for energy and is an important intermediate in lipid synthesis and the formation of acetylcholine, crucial to the transmission of the nerve impulse. This section has synthesized a new compound, fluoroacetyl coenzyme A, which holds promise of explaining many of the activities of the naturally occurring analogue (NINDB L-43). A final step in the study of brain lipids is to relate this basic biochemical information to the specific problem of how particular brain lipids are synthesized. This will be undertaken in a new study (NINDB L-44) of the biosynthesis of cerebrosides which constitute a large fraction of the brain lipids.

Studies of the metabolism of cells and brain tissue performed <u>in vitro</u>, although of inestimable value to basic understanding of brain chemistry, must constantly be related to the metabolism of the living and thinking brain, whether in health or in disease. This is the central purpose of the Section on Cerebral Metabolism. By means of the nitrous oxide technique developed a decade ago by one of its staff, measurements are being made on the circulation and oxygen consumption of the human brain to study the effects of aging, of anxiety, and of a number of hallucinogenic or therapeutic drugs (NIMH-16). Cerebrovascular disease is one of the leading causes of death and disability while senescence has been shown to be associated with a diminution in the nutrition and metabolism of the brain. Continued work of this section is expected to increase our understanding of these problems. Drs. Sokoloff and Kety are directing a project for the Naval Aero Medical Research Laboratory toward the measurement by means of radioactive krypton of rapid changes in human cerebral circulation which may occur in aerial maneuvers (NIMH-17). A few years ago Dr. Sokoloff of this section demonstrated that in hyperthyroidism, or toxic goiter, the brain did not participate in what before

had been thought to be a generalized increase in body metabolism. Present work of the section seeks to explain this phenomenon by means of studies on the blood-brain barrier and the effects of thyroid hormone on the characteristic features of brain metabolism (NIMH-18). During the past two years Dr. Kety and several colleagues have developed a technique for the measurement of local circulation in the brain and applied it first to studies in normal and anesthetized cats (NIMH-19). Values for blood flow in 30 individual regions of the brain have been obtained for the first time, and many of the findings have been surprising and suggestive of a new approach to local functional activity in the normal state. Studies on various hormones and drugs (serotonin, epinephrine, LSD) as well as the important question of cerebrovascular spasm are contemplated.

Other studies on the metabolism of the nervous system in aging (NIMH-32 and 33) and on various chemical components of individual cells and tissues (NINDB L-16, L-17, L-18, and L-19) are described elsewhere.

FUNDAMENTAL STUDIES ON HORMONES AND DRUGS

Although pharmacology and endocrinology have made important practical contributions in the past several decades, our information to date concerning the action of hormones and drugs is largely descriptive. Little is known of the fundamental mechanisms whereby these endogenous and exogenous agents exert their effects and yet it is just such information which is needed for the synthesis of new drugs developed to produce specific therapeutic effects. It was with this concept in mind that the Laboratory of Cellular Pharmacology was established this year to investigate the enzymatic and other biochemical mechanisms of drug and hormone synthesis and their action in the body. Studies of cell metabolism and cellular function as a whole, involving a variety of different techniques and approaches, appear to be the only means of acquiring a definitive understanding of the mechanism of drug action.

The present and projected activities of the laboratory fall within three main areas: Studies on biological methylation; studies in comparative biochemistry; and studies on the interrelation between amino acid metabolism and the tricarboxylic acid cycle. These three areas are not entirely separate but, in fact, overlap to a considerable extent so that the individual projects to be described separately emerge from a broad continuum of common interest and background. For this reason and also because of its recent organization, the laboratory has operated as a unit and has not yet been divided into sections.

The biological methylation mechanisms appear to be of particular interest in cellular pharmacology. It is well-known that methylated compounds like acetylcholine, epinephrine and others play a fundamental role in neurophysiological phenomena such as conduction and transmission of the nerve impulse and that the chemical structure of many drugs having marked neuropharmacological activity (e.g., nicotine, morphine, bufotenin, eserine, etc.)

reveal the presence of a methyl group attached to an nitrogen, sulfur, or oxygen atom. At the present time the most satisfactory working hypothesis suggests that the methyl group in all these cases is derived from the amino acid, methionine. On the basis of the well recognized work of Dr. Cantoni, Chief of this Laboratory, it seems clear that the activation of methionine by energy-rich phophorus compounds is a prerequisite to the transfer of its methyl group. An elucidation of the enzymatic mechanism of this reaction (NIMH-21) would therefore be a great advance in our understanding of the importance of methylation mechanisms in cellular metabolism and, specifically, in brain metabolism. Moreover, the significance of the reaction catalyzed by the methionine activating enzyme is not limited to transmethylation but is of importance in the area of energy metabolism and, as such, is of general biological interest. Many of the drugs such as morphine and mescaline, which act on the central nervous system, contain in their molecule a specific methyl-oxygen or methoxy group. Furthermore, alteration of this structural feature leads to changes in the pharmacological activity of the drug. Little is known of the biological origin of these methoxy groups and any information gained in this connection (NIMH-22) will be useful, leading perhaps also to a better appreciation of the basis upon which the pharmacological effects on the central nervous system are founded. In general, chemical compounds containing a positively charged nitrogen or sulfur atom ("onium" compound) have profound effects, both inhibitory and excitatory, on neural tissue, and have found extensive pharmacological application. The existence of an intimate relation between "onium" compounds, e.g. acetylcholine, and normal neural function is certain. The contemplated studies of the biochemical mechanism for formation and utilization of this type of chemical agent (NIMH-23) are likely to increase understanding of normal and deranged neural function.

The problem of selective toxicity or specificity in pharmacological response must be regarded as the central problem in pharmacology. It has been recognized for a long time that chemotherapy and selective toxicity are intimately related, yet a definition of the problem of specificity of pharmacological response in terms of enzyme mechanisms has not been formulated clearly and has been demonstrated even less adequately. Probably this specificity is related to the fact that the enzymatic equipment of different cells and tissues is different. Generally, it is agreed that quantitatively and qualitatively the enzyme composition of different cells and tissues varies considerably and that it is related closely, though not always obviously, to cellular function. However, it has not been generally appreciated that in different tissues of a single animal species, or in the same tissue of different animals, enzymes which catalyze the same reactions may be different also. If specificity of drug action is to be related to discrete differences in the enzymatic make-up of different cells or tissues, more investigations are required in the field of comparative enzymology. A steady, long-range effort in this direction is required (NIMH-25) and early spectacular results are not to be expected. However, studies of this kind may provide in due course a basis for a more rational approach to drug therapy. Moreover, it is possible that some insight might be gained through this type of approach into the problem of the nature and mechanism of enzyme synthesis.

The third phase of the activity of this laboratory is in the relationships between the intermediary metabolism of carbohydrates and amino acids (NIMH-24), a study recently begun by Dr. Seymour Kaufman. There are numerous examples of how progress in the field of intermediary metabolism has provided a clearer picture of certain biological phenomena. The elucidation of the mechanism of anaerobic glycolysis, for example, has had a profound impact on our understanding of the process of muscular contraction. Besides the possible contribution of this study to fundamental biochemistry, the recent use of certain amino acids in the therapy of mental retardation and convulsive states suggests the need for further research in their metabolism.

Future research in this area, besides the prosecution of the projects already planned and initiated, should include investigations on the mechanism of synthesis of alkaloids and other drugs by plants and the production and metabolism of animal hormones (NIMH-27). Little is known of the relationship between alkaloids and closely related compounds such as the vitamins or coenzymes. However, similar metabolic origin is strongly suggested and this, in turn, indicates the possibility of close physiological relationship between vitamins and alkaloids. Such a program, in the light of recent advances in enzyme chemistry and intermediary metabolism, appears to have excellent prospects of yielding valuable information.

STUDIES ON DRUG ADDICTION

The Addiction Research Center of the National Institute of Mental Health, under the leadership of Dr. Harris Isbell, at the Public Health Service Hospital in Lexington, Kentucky has continued its important and useful work on the mechanisms of narcotic addiction and the testing of new analgesic drugs for addictive liability.

Addiction Liability Testing. This particular phase of the activities of the Addiction Research Center is carried out as a public service. As new drugs are developed by the pharmaceutical industry they are sent to the Center by the Committee on Drug Addiction and Narcotics of the National Research Council for evaluation of their addictive properties. Drugs which are shown to be addictive are placed under the provisions of the Federal Narcotic Acts by proclamations of the President. During the year (NIMH-43) nine new analgesics were evaluated; four of these proved to have addicting potentialities and five were devoid of such action. Studies on four other new analgesics are currently in progress. The properties of three new morphine antagonists were also evaluated. Chief interest in this project continues to be focused on the morphine antagonists and on mixtures of analgesics and antagonists.

Part of the addiction liability testing program is carried on in collaboration with the Department of Defense and designed to develop a synthetic substitute for codeine. Such a substitute is needed in order to free the nation from the necessity of stockpiling opium against the possibility of war. The most significant development in this project was the finding that narcotine is devoid of addiction liability. This substance has been shown to

suppress cough in animals and its clinical antitussive value is now being investigated elsewhere. Narcotine is the second potential substitute for codeine developed through this program.

Chronic Barbiturate and Alcoholic Intoxications. It was found that an occasional patient who had been taking 0.6 gm. of secobarbital or pentobarbital daily would develop convulsions or a mild delirium following abrupt withdrawal of the barbiturate. The incidence and severity of symptoms following withdrawal of barbiturates after intoxication with 0.4 gm. daily is now being determined. The ultimate purpose of this project (NIMH-45) under Dr. Fraser is to determine the minimal level of barbiturate intake which will create a definite degree of physical dependence.

Electroencephalograms obtained during a cycle of experimental alcoholic intoxication for the previous year were completely analyzed. A definite pattern, which paralleled the development of "metabolic" and "tissue" tolerance, was detected. It was also shown that substitution of alcohol for barbiturates in persons strongly addicted to barbiturates decreased the expected incidence of paroxysmal activity, indicating partial physiological equivalence of chronic barbiturate and alcoholic intoxications.

Emphasis in the field of barbiturate and alcoholic intoxications is being shifted from clinical investigations to laboratory studies, using animals, in the hope of developing a better understanding of the pathologic physiology of these conditions and in the hope of developing means for evaluating various therapeutic regimes.

Intoxications Other Than Analgesics, Barbiturates, and Alcohol. Chief interest in this field has been centered on the hallucinogenic drug, LSD-25 (diethylamide of lysergic acid). Acute intoxication with this drug has been termed "experimental schizophrenia," but practically no chronic work has been done with it. In patients studied by Dr. Isbell (NIMH-44), the drug induces a characteristic syndrome mimicked in toto only by mescaline. Although isolated symptoms which occur in schizophrenia are observed during acute LSD-intoxication, the total symptom-picture does not entirely resemble that of schizophrenia. Definite relationship between the size of the dose of LSD-25 and the degree of "mental" and "non-mental" effects was observed. LSD produces distinct changes in the Minnesota Multiphasic Personality Inventory, consisting of statistically significant elevation on the Pt (psychasthenia), Sc (schizophrenia), Pa (paranoia), SI (social introversion), and the Taylor Anxiety Scale. During chronic administration of LSD, the original spectacular effects can no longer be obtained after two or three days administration of one dose daily. Once this tolerance has developed, it is not completely overcome by increasing the dose as much as four times. Tolerance is lost as rapidly as it is developed since the degree of LSD-effect reaches levels observed prior to chronic intoxication after three days of abstinence.

During the coming year, it is expected that much less work will be done with LSD. Trial of the drug, bufotenine, which is chemically related to

serotonin and induces symptoms in the monkey resembling those caused by LSD, will be made. Investigations of the cardiovascular effects of some drugs in the cannabinol (marihuana) group will be undertaken. Studies on the psychological effects of some sympathomimetic amines will be initiated.

Biochemistry of Addiction. Work in this field under Dr. Eisenman continued to be centered on the changes in the functions of the endocrine system induced by acute and chronic administration of morphine (NIMH-46). Previous experiments had shown that morphine depressed the excretion of 17-ketosteroids in male patients and that withdrawal of morphine was followed by a marked "rebound" in excretion of these substances. During the current year, we have found similar changes in the excretion of the corticoids derived solely from the adrenal glands during morphine addiction and withdrawal. Evidence suggestive of a decrease in the excretion of pituitary gonadotropin was also obtained. The activities of the biochemical unit will probably soon be shifted to the fields of drug metabolism and enzymology.

Neuropharmacology of Chronic Drug Intoxication. It was found by Dr. Wikler and his colleagues that the development of physical dependence on morphine in chronic spinal animals is completely prevented by the administration of large amounts of Nalorphine every three hours. This work (NIMH-48) complements that described above in the section on Addiction Liability Testing with respect to mixtures of analgesics and antagonists. A beginning was made in determining the neuropharmacology of acute and chronic barbiturate intoxication. Attempts to develop physical dependence on alcohol in dogs were initiated during the year but the experiments are incomplete. Trend in the activities of this section will be a gradual shift from studies on analgesic drugs to the elucidation of the mechanisms underlying other drug intoxication.

Experimental and Clinical Psychology of Addiction. In the preceding calendar year, Dr. Hill developed a method for determining the effects of morphine on the conditioned inhibition of a feeding response in rats. His application indicated that morphine was reducing anxiety in the rats in anticipation of a painful stimulus. Specificity of the method has been under test during the current year (NIMH-47). It is hoped that this method will provide another means of testing new drugs for pain relieving properties. It was also demonstrated in man that the effects of morphine and pentobarbital on reaction time were greatly affected by altering the motivation of the subjects used in the experiment (NIMH-47). Such a demonstration of marked variation of drug effects by altering the situation in which the drugs were given is of great theoretical and practical importance.

Plans for the coming year include extension of the experiments on the effect of motivations on drug effects, beginning of attempts to condition phenomena of physical dependence, and the development of inventories for assessing the subjective effects of the classes of drugs in which the NIMH Addiction Research Center is interested.

DEVELOPMENT, REGENERATION, AND AGING OF THE NERVOUS SYSTEM

A group of related properties of the nervous system, important not only for their fundamental nature but also because they are intimately involved in certain mental and neurological problems of national significance, are its ability to grow, its commonly accepted inability to regenerate, and its tendency to mature and grow old and less effective. Several groups of investigators in the Basic Research Program are attacking many phases of these associated problems.

Development and Regeneration. Dr. William Windle, Chief of the Laboratory of the Neuroanatomical Sciences and well-known as a neuroembryologist even before his recent and promising research on nervous regeneration, has organized an important Section on Development and Regeneration primarily concerned with these problems. During the past year he has initiated a systematic study of the embryological development of certain fiber tracts and nuclei in the human embryo based upon material which has been collected during the past twenty years and prepared by certain silver staining methods to bring out finer details of neuron growth (NINDB L-8). Knowledge of the intrinsic development of the human brain is fundamental to a clear understanding of adult brain anatomy and physiology, yet little is known of this intrinsic structural development at present.

Certain aspects of the "doctrine of specific nerve energies" are being re-examined. When mammalian peripheral somatic nerves are cut and transposed in such a way that fibers of one are directed in their regeneration toward the end organs of another, it is held that no functional restitution ensues. The end organs appear to be incapable of inducing neuronal specificity in the nerve in question, at least in mammals, although this process has been shown to occur readily in certain lower forms. The situation has not been adequately examined and put to scientific tests in the case of the autonomic nerves in mammals. Studies during the past year by Dr. Guth of this laboratory (NINDB L-14 and L-15), involving transplantation of the central stump of the severed vagus nerve of the cat into the sympathetic trunk so that the fibers regenerated toward the superior cervical sympathetic ganglion, revealed some functional restitution. Vasomotor reflexes became re-established by preganglionic parasympathetic neurons which formed synapses with postganglionic sympathetic neurons in the superior central cervical sympathetic ganglion, indicating that even in mammals one nerve may be made to regenerate and substitute for another.

Abnormalities in fetal or neonatal development may be responsible for certain types of cerebral palsy and mental retardation. A project on which little new work has as yet been done has to do with asphyxia during birth and its effects upon the structure and function of the brain (NINDB L-9). The initial experiments, carried out several years ago, demonstrated in guinea pigs that neuromuscular disorders resembling certain aspects of cerebral palsy in man resulted from asphyxia neonatorum. Furthermore, impairment of intelligence and learning ability was demonstrated in animals which had recovered from the neuromuscular disorders. This direct evidence that

asphyxiation at birth, not only can lead to cerebral palsy but may also be one of the causes of mental defectiveness, needs to be explored further. Within a short time additional experiments along this line will be in progress and effects of obstetrical anesthetics will be studied. There is reason to expect that this type of research will point a way to preventive measures in man.

Dr. Gordon Allen in a cooperative study at the New York Psychiatric Institute with Dr. Franz Kallman, a noted authority upon the genetics of mental disease, has been investigating the genetic and congenital aspects of mental deficiency by studies upon twin families in which one or both members of the pair have been diagnosed as mentally defective. During the past year he has increased the number of cases in his sample to 539 sets of twins, 12 sets of triplets, and 2 sets of quadruplets (NIMH-63). The careful clinical and psychological tests of these individuals along with studies of their blood grouping are still continuing and statistical analysis of the results will be made during the forthcoming year.

Research on the subject of regeneration in the central nervous system constitutes a major endeavor of Dr. Windle's laboratory and was the first project to be activated. The subject has been reviewed recently by 33 participants to a conference held at the NIH in May 1954. A monograph with complete bibliography is now in the process of publication (NINDB L-2). Central nervous regeneration occurs readily in certain lower forms of animals, such as amphibians, but does not occur readily in mammals and is said not to occur in man. It has been found possible to bring about some regeneration in the severed spinal cord of adult cats and dogs by administering drugs which act partly to inhibit the formation of glial barriers and thus permit the regenerating neurons to traverse the site of the damage (NINDB L-3). An effort is being made to extend this work to the point of bringing about functional restitution but no striking success has as yet been achieved. A number of related aspects of the problem are being investigated (NINDB L-3, 4, 5, 6, 7, 12, 22). The significance of this research can best be illustrated by pointing out that there are about 100,000 paraplegic individuals in the United States who have required or still do require a great deal of hospitalization. It is estimated by the Liberty Mutual Insurance Company of Boston that the cost of indemnity and continuous hospitalization of a single paraplegic patient would amount to $400,000. Should it ever become possible to induce functional neuronal regeneration in patients of this type, incalculable savings in human resources and money may be effected.

These studies on the anatomical and genetic aspects of the development of the nervous system are paralleled by studies in the Laboratory of Psychology on the factors responsible for the development of personality and other psychological aspects of the problem. These are included in the report of Clinical Investigations, NIMH.

Aging of the Nervous System and of the Mind. The Section on Aging, under Dr. James Birren, in the Basic Research Program is continuing to investigate many of the aspects of this problem from the anatomical, biochemical, and psychological points of view. With the help of the animal production facilities

of NIH, he has raised a colony of aged rats corresponding in many aspects of their behavior to human beings at the end of the normal life span. In the past year he has begun quantitative measurement of certain aspects of the behavior of these animals and has shown a marked slowing in the reaction time (NIMH-28). These changes can be compared with similar changes which this investigator has found in aging human beings (NIMH-29).

In a recent publication, Dr. Seymour Kety of the Section on Cerebral Metabolism, Laboratory of Neurochemistry, pointed out on the basis of his own work and that of others that there was a progressive fall in the blood flow and the metabolism of the human brain with advancing age (NIMH-16). This section and the Section on Aging are now collaborating with Dr. Perlin of the program in Clinical Investigations on a long-term study which will correlate in the same individual measurements of cerebral blood flow, cerebral metabolism, and certain psychological attributes such as perceptual abilities and personality structure (NIMH-30). These observations on the brain as a whole are being paralleled by Dr. Streicher, who is investigating certain biochemical functions in brain tissue in vitro as a function of age (NIMH-32 and 33). In the field of the structural changes associated with aging, Dr. Birren is undertaking a careful quantitative study of the histological changes in the nervous system as a function of age, by careful counts of cellular population, blood vessels, and measurement of extracellular space (NIMH-31). Surprisingly enough, quantitative data upon this subject are woefully lacking. A study on the hemodynamic factors concerned with the formation of cerebral hemorrhage, one of the most common causes of death among the elderly, is being pursued by Dr. Cammermeyer of the Laboratory of Neuroanatomical Sciences (NINDB L-20).

PERCEPTION AND BEHAVIOR

Research into the basic mechanisms involved in perception, learning, and behavior are encompassed in the program of the Laboratory of Psychology recently set up in both the Basic Research Program and in the program of Clinical Investigations of NIMH under Dr. David Shakow, a distinguished psychologist. The function of psychology in these areas and, for that matter, in the whole field of mental health is in one sense central. This is not meant in the sense of being more fundamental or basic, but rather in the sense of being at that level of organization where it can serve as a cross-road for many disciplines or a bridge between two. Because of its special history -- its concern with both measurement on the one hand and with gross behavior on the other -- it can serve as a bridge between disciplines such as biology and sociology or between physiology and psychiatry.

Studies of the Section on Perception and Learning -- the effects of LSD on visual functions (NIMH-38-C) and the recording of eye movements (NIMH-40) -- have been discussed under the Special Senses. Dr. Blough, recently appointed to this laboratory, has developed a technique capable of yielding continuous threshold measures for visual discrimination in an unrestrained animal. This technique will be further developed and applied to studies of vision in pigeons in an effort to identify basic mechanisms of

discrimination learning (NIMH-42). A similar study of discrimination learning in normal man is being undertaken (NIMH-41).

Two important psychological theories of normal perception have been promulgated in recent years -- that of Köhler and that of Hebb. In many respects, these two theories are alternative rather than complimentary and Dr. Carlson has designed a study which should provide an important source of evidence for deciding between the two (NIMH-39). In order to understand fully the distortions in perception which are found in mentally deranged patients, it is necessary to have a sound theory of the normal processes of perception.

In the past year a Section on Animal Behavior has been organized under Dr. Enger Rosvold, who is preparing a colony of primates for future studies. Continuing the work which he successfully carried on at Yale, this section will investigate the relationship between brain function and behavior by means of neurosurgical, neurophysiological, endocrinological, and psychological techniques (NIMH-37). During the past year, he has shown that calculated changes in brain cause changes in behavior which can be reliably measured. Specifically, it has been possible to demonstrate differential effects of various lesions on intelligence, emotional behavior, and group behavior. The section has also been developing a continuous performance test and improving its design in the hope that it will reliably discriminate subjects with brain damage from normal subjects (NIMH-36). Preliminary findings indicate that the test can be successful under certain conditions. Since there is not now available any easily administered objective test which will demonstrate the effect of brain damage on serial function, such a development appears promising.

For a considerable time more, the discipline of psychology will have to wage a constant struggle with the problems of pinning data down to say nothing of the problem of pinning the questions down. This will be reflected in the work of the Laboratory of Psychology. Within its wide range of studies it will be seen that much time is devoted to methodological problems as well as to substantive ones. Other research of this laboratory is reviewed under the report of Clinical Investigations, NIMH.

HUMAN RELATIONS

Basic research in the complex and difficult field of human relations is under the able leadership of Dr. John Clausen, Chief of the Laboratory of Socio-environmental Studies. During 1954, this laboratory was brought substantially to full personnel strength and the scope of research undertaken was broadened, with the initiation of several small-scale projects on problems of methodology and on social interaction within treatment settings.

A major project of the laboratory is a study of the impact of mental illness upon the family of the patient (NIMH-49, 50, 51, and 52). This study which has largely concentrated upon the wife's attitudes and behavior is in the stage where data are still being collected and the results are

primarily descriptive and preliminary. However, the effects of the illness upon the wife's orientation and communication with other persons has been analyzed and correlated with the wife's educational status, acceptance of the diagnosis, and the amount of affection expressed by the wife for her husband. There is evidence that attempts at concealment added appreciably to the psychological stress experienced by the wife. This study has special relevance to problems of society's recognition and treatment of pre-hospitalized mentally ill individuals, to questions of hospital procedures in providing the kinds of help that patients' families need, and for an understanding of problems of rehabilitation of the discharged mental patient. Drs. Yarrow and Jordan of this laboratory have initiated a much needed study on the validity of retrospective data on parent-child relationships (NIMH-53). This is a carefully controlled and critical analysis of the validity of such data upon which much investigation in psychiatry has depended.

Drs. Clausen and Kohn have in the past year completed two phases of their long-term study of social, demographic, and health factors relating to mental illness in Hagerstown (NIMH-55). The source of the data consisted of interviews with all available persons hospitalized for schizophrenia from Hagerstown during a twelve-year period and similar interviews with a carefully selected control group. This important matching procedure was made possible by earlier Public Health Service studies and their records in Hagerstown. Two important findings have emerged -- one, that social isolation does not seem to be a predisposing factor in schizophrenia, but appears to be the result of prior difficulties in interpersonal relationships, a consequence rather than a cause of developing illness. Secondly, these studies confirmed and amplified previous and less rigidly controlled findings reporting that the mother of the schizophrenic patient has typically played a very strong authority role and his father a very weak one toward the child.

Three small-scale studies of social interaction within the wards of the Clinical Center were undertaken within the latter half of the year (NIMH-58-C, 59-C, and 60-C). Dr. Goffman has been investigating norms regulating social interaction among patients and personnel through direct participation with patients on a ward. Dr. Deasy has been studying the way in which nurses treat their patients as related to the "reputation" of the patient among the nursing staff, and Mrs. Schwartz has investigated the changing perception which nurses have of patients and of their duties when the traditional role of the nurse is redefined by the ward administrator. Dr. Youmans is engaging in a study (NIMH-61) which seeks to relate the career patterns of selected administrative personnel to social origins, levels of aspiration, attitudes toward supervisory practices, and authoritarianism, and an index of psychological stress. A study of social psychological factors in juvenile delinquency (NIMH-57) and of the social factors which produce vulnerability to psychological stress (NIMH-56) are about to be initiated.

The laboratory took advantage of the availability of vaccination against poliomyelitis in a local community to study the social and psychological factors relating to the acceptance of a public health program (NIMH-62). Interesting and significant correlations were found between the

attitudes toward such public health programs, ability to assess their objectives, inclination to seek professional guidance, and the socio-economic and educational scales of the families. Knowledge of such relationships, especially when placed upon a statistically significant basis rather than upon the hunches which often prevail, are of value in designing public health programs of various sorts for the general population.

TECHNICAL DEVELOPMENT

Throughout this program, as in the history of science generally, it is apparent that many important advances in understanding come about only with the development of the proper tools and methods of research. Tc assist the scientists in perfecting their techniques and to collaborate with them in the elaboration of new ones, the Section on Technical Development was established. Its Chief, Michael Davis, combines the skills and training of an electronics engineer and a neurophysiologist. Besides the routine duties of repair and maintenance (NIMH-65), the section has designed, developed, and constructed a wide variety of instruments, not previously available, for the specialized purposes of the research program (NIMH-67). These have included techniques for communication and recording useful to the clinical programs in psychiatry and neurosurgery, apparatus for psychological studies, and the complex electronic instruments important to research in neurophysiology and biophysics. The section has developed instruments for the delicate task of guiding microelectrodes through the nervous system and into individual cells with a precision expressed in thousandths of a millimeter. An analogue computer capable of solving complicated equations such as those involved in measurement of local blood flow in seconds instead of hours is under construction.

This list by no means exhausts the contributions of this section or of the program as a whole to the creation of new tools for research. In every laboratory new techniques are being developed, improved and modified and then applied to yield new information and create better understanding of the basic processes responsible for mental and neurological function.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Nonsectional 4. 5. NINDB L-1

6. Organizational Project

7. W. F. Windle

8. Secretarial personnel

9. PROJECT DESCRIPTION.

The Chief of the Laboratory of Neuroanatomical Sciences reported for duty on January 4, 1954. An existing research project was transferred from Morton Grove, Ill., to Bethesda, Md., on January 27 and 28. A room in Building 14 was made available on a loan basis for a short time to house the animals which were brought from Morton Grove. Research activities began in that space. Time during the early part of the year was spent mainly in recruiting staff, ordering equipment and planning research activities of the laboratory.

On March 1, 1954, Dr. Jan H. W. Cammermeyer, Chief of the Section on Experimental Neuropathology, reported for duty. Temporary laboratory and animal space was provided in Building T-6 on May 3, 1954; additional research projects were activated at that date. Several members of the scientific staff, Drs. Lloyd Guth, Leo C. Massopust, Jr., Milton W. Brightman and R. Wayne Albers, arrived between July 1st and September 15th. On November 1, Dr. Grant L. Rasmussen reported for duty as Chief of the Section on Functional Neuroanatomy. Exhibit 1 illustrated the results of this project on organization as of the end of the calendar year 1954. It should be noted that negotiations are under way for a many to occupy the post of Chief of the Section on Neurocytology, as well as for two scientists of professional grade to complete the unit investigating cerebral palsy.

It is hoped that some activities of the laboratory can be transferred to quarters in the Clinical Center in January 1955. Plans for rehabilitation of Building T-10 began to be laid in June 1954, and activities along this line proceeded during the following months of the year. Completion of this space is not anticipated before December 1955; space will be retained in Building T-6 until that time.

Proposed course of project: It is estimated that the activities of this project are about 3/4 completed. The project should be terminated in 1955.

R.P.C.-2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB
L-1
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$6,000	1	2	3	-	1	1	
FY 1956	0,000			-	-	-	-	

12. BUDGET ACTIVITY: Research

13. No co-operating units

14.

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Development and Regeneration. 4. 5. NINDB L-2

6. Editorial project

7. W. F. Windle

8. Secretarial and library personnel

9. PROJECT DESCRIPTION.

Objectives: To prepare for publication a Monograph entitled "Regeneration in the Central Nervous System". To compile a comprehensive bibliography on this subject.

Accomplishment: Early in 1954 it was decided in meeting with Drs. Bailey, Roty and Stone, to hold a conference of investigators interested in the subject of regeneration in the central nervous system. The objective was to bring together and correlate existing information prior to embarking upon research in this field in the Laboratory of Neuroanatomical Sciences. The National Advisory Neurological Diseases and Blindness Council provided a chairman's grant to finance the conference.

At the conclusion of the conference in May, the Chief of this laboratory was asked to serve as editor of the proceedings and to put them into such form as could be published and made available to the scientific public. Exhibit II shows the title page of the monograph which was sent to the publisher on December 7, 1954. In addition to providing a comprehensive survey of the subject of regeneration in the central nervous system, the monograph contains a bibliography which includes all known literature references.

Proposed course of project: Correction of proof and preparation of an index remain to be done during 1955. Royalties which may accrue will be given, by the publisher, to the NIH and will be used to reimburse the chairman's grant.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NIMDB
L-2
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patients Days
FY 1955	$5,000	1	2	3	-	1	1	
FY 1956	0,000	-	-	-	-	-	-	

12. BUDGET ACTIVITY: Research

13. No co-operating units

14.

R.P.C. -1
December 1954 Ayalysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Development and Regeneration. 4. 5. NINDB L-3

6. Regeneration of the transected spinal cord of the adult cat.

7. W. F. Windle

8. Junior personnel of section

9. PROJECT DESCRIPTION.

Objectives: To bring about anatomical and physiological regeneration in the acutely transected spinal cord of the adult cat. To bring about functional restitution as a result of this regeneration.

Methods employed: The spinal cord of the adult cat is surgically transected at the lower thoracic or upper lumbar level. After this, extraordinary methods of animal care are necessary on a daily basis to maintain these spinal animals in first class condition. Certain pyrogenic bacterial polysaccharides are administered intravenously to inhibit formation of a glial barrier or, in other ways, to promote a condition favorable to regeneration of central nerve fibers across the transection site. As a rule two cats are operated at each session, one receiving no therapy and serving as a control for the other which is given the pyrogen. Comparison of the subsequent events in respect to neurological improvements is made from time to time and recorded in 3-D motion pictures.

Major findings: Findings in the current series tend to be confirmatory of earlier experiments carried out prior to the establishment of the Laboratory of Neuroanatomical Sciences. One new observation: phenomena resembling those encountered in spinal cats receiving intravenous pyrogen therapy occurred in an animal which postoperatively contracted a urinary tract infection with an organism known to produce bacterial pyrogens.

Significance: The studies form a basis for possible therapy in acute human paraplegias. At the present time there is little other than physical rehabilitation that can be done for the patient with a severed spinal cord. If a way can be found to obtain even the least amount of regeneration in the human spinal cord, such as has been demonstrated in animals, the prognosis for the acute spinal cord injury patient should be improved.

Proposed course of project: It is planned to continue this project vigorously. More emphasis will be placed on an effort to re-establish function after spinal cord transection. The Section on Spinal Cord in the Laboratory of Neurophysiology expects to collaborate in this study.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB
L-3
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions			Man Years			Patient Days
		Prof	Other	Total	Prof	Other	Total	
FY 1955	$5,000	1	7	8	0.5	0.5	1.0	
FY 1956	$6,750	1	7	8	0.5	0.5	1.0	

12. BUDGET ACTIVITY; Research

13. No co-operating units

14.

R.P.C. -1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Development and Regeneration 4. 5. NINDB L-4

6. Residual function after subtotal spinal cord transection in the cat.

7. W. F. Windle

8. Junior personnel

9. PROJECT DESCRIPTION.

Objectives: To produce subtotal transections of the spinal cord, leaving intact only a small number of nerve fibers in the ventral funiculi. To compare residual functional activities of such animals with activities acquired by animals in which total spinal cord transection had been followed by regeneration of nerve fibers induced by treatment with bacterial pyrogens.

Methods employed: In one series of cats, surgical dissection through the spinal cord at the level of the lower thoracic or upper lumbar region resulted in section of all nerve fibers except a few on either side of the median raphe in the ventral funiculi. In another series of cats, the cord was transected completely and therapy with various bacterial pyrogens instituted postoperatively. Observations were recorded in 3-D motion pictures.

Major findings: The animals with complete spinal cord transection have not as yet exhibited regeneration. Animals with less than 5% of the white matter of the ventral funiculi remaining intact, have no retension of sensory modalities but have retained certain reflexes and motor functions, including some locomotion, comparable to animals of a previous series in which some regeneration in the spinal cord had taken place

Significance: The experiments give us a base against which to compare the early signs of regeneration in pyrogen treated spinal animals undergoing regeneration.

Proposed course of project: The project will be continued through next year with a larger number of animals and a longer time for observation. Ultimately the material collected from the animals will be subjected to histological analysis.

R.C.P. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB
L-4
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$5,000	1	4	5	0.5	0.5	1.0	
FY 1956	6,750	1	4	5	0.5	0.5	1.0	

12. BUDGET ACTIVITY; Research

13. No co-operating units

14.

R.P.C. -1 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Development and Regeneration 4. 5. NINDB L-5

6. Activities of bacterial pyrogens

7. W. F. Windle

8. Junior personnel

9. PROJECT DESCRIPTION.

Objectives: To elucidate a mechanism of action of a pyrogenic bacterial polysaccharide which is being used to induce regeneration in the central nervous system. Specifically, to learn whether or not the drug piromen is capable of significantly altering certain characteristics of the ground substance of young ear cartilage, with the purpose of developing a reliable test for its efficacy in regeneration experiments.

Methods employed: Rabbits at weaning were divided into three groups: those receiving no therapy; those receiving therapy intravenously with a low dose regimen to the drug; and those receiving a high dose regimen of the drug. The low dose regimen was that which previously had been demonstrated to be optimum for promotion of healing processes after spot burns. Therapy was administered for 1, 2, 6, 10, 14 and 21 days. Pieces of the ears were removed for histochemical study at these times. Subsequently, pieces of the scars which had been created by this removal were removed on days 35 and 41 and treated similarly.

Major findings: No alteration in mucopolysaccharide content of the ground substance of growing ear cartilage of the rabbit could be demonstrated. No alteration of the healing cartilage scar in the rabbit ear could be demonstrated.

Significance: Results raise a question of possible inactivity of the lot of drug supplied.

Proposed course of project: It is expected that activities of other bacterial pyrogens may be investigated next year.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB
L-5
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions			Man Years			Patient Days
		Prof	Other	Total	Prof	Other	Total	
FY 1955	$5,000	1	4	5	0.2	0.3	0.5	
FY 1956	6,750	1	4	5	0.5	0.5	1.0	

12. BUDGET ACTIVITY; Research

13. No co-operating units

14.

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Development and Regeneration 4. 5. NINDB L-6

6. Evaluation of prognosis for cord regeneration in acute cases of human paraplegia.

7. W. F. Windle

8. Milton G. Shy and staff

9. PROJECT DESCRIPTION.

Objectives: To evaluate reports in the literature on regeneration in the human spinal cord. To study one human case of spinal cord severance in which treatment with the drug piromen was instituted within a few days after the transection.

Methods employed: Clinical observation and correlation with animal experiments.

Major findings: A. There is only one report in literature of a human subject with severed spinal cord in which conditions were at all comparable to those in animal experiments. In this there was some evidence of regeneration having taken place after sectioning the severed spinal cord. This case has been reviewed in the forthcoming monograph on "Regeneration in the Central Nervous System". B. One patient is under observation at present.

Significance: Establishment of the possibility of some spinal cord regeneration in man, even though it may be slight, will radically alter our approach to the subject.

Proposed course of project: Continuation of observations with addition of subjects if and when available.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB
L-6
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$5,000	1		1	0.5		0.5	101
FY 1956	6.750	1		1	0.5	0.5	1.0	

12. BUDGET ACTIVITY; Research

13. No co-operating units

14.

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Development and Regeneration 4. 5. NINDB L-7

6. Relation of age to regeneration in stab wounds of the brain

7. W. F. Windle

8. Junior personnel

9. PROJECT DESCRIPTION.

Objectives: To determine whether or not intracerebral nerve fibers can regenerate across a simple stab lesion in the brain in newborn and young kittens. To relate this to possible inhibition of glial barrier formation brought about by administration of bacterial pyrogens.

Methods employed: In kittens one hour to three weeks old, a simple stab wound into the cerebrum was inflicted under local anesthesia. Half of each litter received pyrogen therapy; half were controls. An attempt was made to keep the animals alive and in good health for a period of seventy days; some died earlier. The animals were killed by the profusion fixation technique; the brains were dissected out and studied grossly; blocks of tissue at appropriate sites were removed and are being prepared by several neurological staining techniques.

Major findings: There appears to have been less adhesion formation in those kittens which had received pyrogen therapy. No microscopical findings to report.

Significance: Whether or not regeneration in the mammalian central nervous system occurs more readily in the newborn and very young individual than in the adult is a moot question. The only investigation comparable to this one was carried out on rats in 1903, prior to the time when adequate neurological staining methods were available.

Proposed course of project: The course of the project will depend upon histological observations of the present series.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB
L-7
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$5,000	1	4	5	0.2	0.3	0.5	
FY 1956	6,750	1	4	5	0.5	0.5	1.0	

12. BUDGET ACTIVITY; Research

13. No co-operating units

14.

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Development and Regeneration 4. _____ 5. NINDB L-8

6. Development of fiber tracts and nuclei in the brain in human embryos

7. W. F. Windle

8. _____

9. PROJECT DESCRIPTION.

Objectives: To observe and describe the genesis and subsequent development of nerve fiber tracts and groups of nerve cells in the human brain and spinal cord.

Methods employed: The method of microscopical observation is employed in serial sections of the human embryos which have been collected during the past twenty years and prepared by certain silver staining methods to bring out finer details of neuron growth.

Major findings: A renewed study of the origin and migration of primary motor cell groups of the brain stem has shown that all visceral motor nuclei arise in a location adjacent to the floor plate of embryos 4-6mm long (end of the fourth week of gestation). These nuclei migrate to more lateral positions in embryos 12-14mm long (between the sixth and seventh weeks). This migration gives rise to the genu of the facial nerve and to similar bundles of fibers of much smaller size in the trigeminal, glossopharyngeal and vagus nerves.

Significance: Knowledge of intrinsic development of the human brain is fundamental to a clear understanding of adult brain anatomy and physiology. Little is known of intrinsic structural development at present.

Proposed course of project: The study of these human embryos will be continued throughout the coming year. It is hoped that additional human embryos can be obtained and subjected to silver staining.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB L-8 Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$5,000	1		1	0.5		0.5	
FY 1956	6,700	1		1	0.5		0.5	

12. BUDGET ACTIVITY: Research

13. No co-operating units

14.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Development and Regeneration 4. 5. NINDB L-9

6. Effects of anoxia at birth on brain structure and function

7. W. F. Windle

8. Jan H. W. Cammermeyer; other personnel to be recruited

9. PROJECT DESCRIPTION.

Objectives: In animals to simulate the abnormal neuromuscular behavior known in man as cerebral palsy. To determine effects of anoxia during birth on brain structure and on learning ability. Similarly, to determine effects of obstetrical anesthetic agents.

Methods employed: Experimental surgical approach in pregnant guinea pigs to asphyxiate the young; resuscitation of the newborn followed by study with methods of experimental neuropathology and experimental psychology.

Significance: The study should form a basis for understanding of the comparable human conditions. It should lead to recommendations concerning ways of preventing certain neurological disorders at birth.

Proposed course of project: The staff on the research team is being recruited at present. It is planned to continue certain experiments begun by the principal investigator several years ago, to extend these and to supplement them with studies in other species of animals, notably primates.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

NINDB

10. L-9
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$25,000	2	2	4	0.9	0.9	1.8	
FY 1956	31,000	2	2	4	1.9	2.0	3.9	

12. BUDGET ACTIVITY; Research

13. No co-operating units

14.

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Development and Regeneration 4. _____ 5. NINDB L-10

6. Relationship between Neurosecretion and milk ejection

7. Milton W. Brightman

8. Junior personnel

9. PROJECT DESCRIPTION.

Objectives: To determine whether or not a depletion of neurosecretory material occurs concomitantly with release of hormones from neurohypophysis in response to various stimuli.

Methods employed: A small breeding colony of mice was established (co-operation with Dr. G. Jay). The mice were allowed to nurse their young for various periods of time under various circumstances. They were killed and the brains were stained by special methods. The amount of neurosecretory material was correlated with the times of suckling.

Major findings: Studies begun at Yale University and continued here have indicated that stimuli of suckling, of behavior associated with suckling, as well as parturition followed immediately by suckling, all resulted in a depletion of neurosecretory material from hypothalamo-hypophysial system.

Significance: These experiments point to a close relationship between the central nervous system and the endocrine system, involving the pathway linking hypothalamus and neural lobe of the hypophysis.

Proposed course of project: About eighteen more experiments must be reviewed histologically. An additional series of 12 litters will be required to complete the project.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

NINDB

10. L-10
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$5,000	1	1	2	0.2	0.3	0.5	
FY 1956	5,4000	1	1	2	0.2	0.3	0.5	

12. BUDGET ACTIVITY: Research

13. No co-operating units

14.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Development and Regeneration 4. _____ 5. NINDB L-11

6. Release of neurosecretory material and of antidiuretic hormone from the hypothalamo-hypophysial system

7. Milton W. Brightman

8. Junior personnel

9. PROJECT DESCRIPTION.

Objectives: To determine whether circulating levels of posterior lobe hormones inhibit or stimulate the output of these hormones and of neurosecretory material from the neurohypophysis itself.

Methods employed: Two groups of rats were used. One group was dehydrated and given peanut oil intramuscularly as a control. The other group, also dehydrated, was given pitressin tannate in oil intramuscularly. The effects of this treatment on the neurosecretory content of the hypothalamus and neurohypophysis were determined.

Major findings: Pilot studies, begun at Yale University and continued in the Laboratory of Neuroanatomical Sciences, indicate that exogenous hormone administered intramuscularly is inactivated too rapidly to affect the hypothalamic nuclei.

Significance: The experimental work points to a close relationship between the central nervous system, particularly the hypothalamus, and the endocrine system through the hypothalamo-hypophysial pathway.

Proposed course of project: The next phase of the project entails construction of suitable indwelling polyethylene catheters for continuous infusion of hormones into the internal carotid artery.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

NINDB

10. L-11
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$5,000	1		1	0.2	0.3	0.5	
FY 1956	5,400	1		1	0.2	0.3	0.5	

12. BUDGET ACTIVITY: Research

13. No co-operating units

14.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Development and Regeneration 4. 5. NINDB L-12

6. Vascular supply of the spinal cord

7. Milton W. Brightman

8.

9. PROJECT DESCRIPTION.

Objectives: To determine the exact arterial supply and venous drainage of the mammalian spinal cord in several species commonly used for laboratory experiments.

Methods employed: A modification of an India ink-gelatin perfusion technique has been used to demonstrate the blood vessels of the spinal cord in the mature rat, cat and in the kitten. The method has been standardized to stimulate normal blood pressure and blood flow of the solution in a manner similar to that during life.

Major findings: No report as yet.

Significance: This project will provide basic information for a more understanding surgical approach to the spinal cord in experimental animals.

Proposed course of project: Application of the techniques to completion of the study in 1955.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

NINDB

10. L-12
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$5,100	1		1	0.5		0.5	
FY 1956	5,500	1		1	0.5		0.5	

12. BUDGET ACTIVITY: Research

13. No co-operating units

14.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Neurocytology 4. _____ 5. NINDB L-13

6. Electron-micrographic exploration of brain structures and function

7. Chief, Laboratory of Neurocytology (appointment pending)

8. _____

9. PROJECT DESCRIPTION.

Objectives: To conduct various studies of the ultrastructure of nerve cells, neuroglia, central synaptic mechanisms and peripheral nerve fiber terminations by the techniques of electron microscopy and micrography.

Methods employed: The electron microscope and other apparatus will be used to extend knowledge in the field of neurocytology.

Major findings: No report as yet. Apparatus is being assembled.

Significance: The techniques employed in electron microscopy and other closely related techniques have undergone extensive development and perfection during the last two or three years. It is proposed to utilize these techniques in an exploratory manner in the Laboratory of Neuroanatomical Sciences. One cannot predict what may develop from this project. Personnel of a research unit, which will be formed, will collaborate with other investigators in the National Institute of Neurological Diseases and Blindness on related projects requiring investigation with the electron microscope.

Proposed course of project: To activate and extend the project in the coming months.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

NINDB

10. L-13
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$40,000							
FY 1956	10,000				0.3	0.4	0.7	

12. BUDGET ACTIVITY: Research

13. No co-operating units

14.

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Neurocytology 4. 5. NINDB L-14

6. Neuronal specificity in the autonomic nervous system in mammals

7. Lloyd Guth

8. Junior personnel

9. PROJECT DESCRIPTION.

Objectives: To determine whether or not end-organ induction of neuronal specificity occurs in the mammalian autonomic nervous system.

Methods employed: The vagus nerve of the cat is anastomosed with the cervical sympathetic trunk in the neck in such a way that regenerating vagal fibers course rostrad toward the superior cervical sympathetic ganglion. Pupillary and vasomotor reflexes are studied during the course of this regeneration. The fiber spectra of the regenerated nerves will be determined histologically at the end of the experiment.

Major findings: Preliminary data suggest that, although a functional synapse has been formed on those cells supplying the pupillary constriction of the eye and the vasomotor fibers of the ear, it is only in the latter (ear vessels) that normal, functional reflexes are restored.

Significance: Prior to this no one has demonstrated the resumption of function following crossed anastomosis of nerves of different specificity in the mammal, although such experiments have been successfully performed in Amphibia.

Proposed course of project: Work on this project will be continued and extended along the same lines throughout the coming year.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

NINDB

10. L-14
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Position Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$5,400	1		1	0.5	0.6	1.1	
FY 1956	5,000	1		1	0.5	0.5	1.0	

12. BUDGET ACTIVITY: Research

13. No co-operating units

14.

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Neurocytology 4. 5. NINDB L-15

6. Fiber spectra in crossed anastomosis of peripheral nerves

7. Lloyd Guth

8.

9. PROJECT DESCRIPTION.

Objectives: To determine whether or not nerve fiber spectra are altered following crossed anastomosis of nerves. For example, does the fiber spectrum of the vagus nerve, when regenerating into the cervical sympathetic trunk, take on the characteristics of the sympathetic trunk or does it retain that of the vagus?

Methods employed: Surgical anastomosis of the vagus and sympathetic trunks in cats, using the arterial sleeve splice to facilitate the regenerative process. Subsequent study of portions of the nerve by special neuropathological techniques.

Major findings: No report as yet. The neuropathological techniques have been successfully developed for the purpose of the study.

Significance: The project will provide fundamental knowledge of structural specificities of nerves.

Proposed course of project: The project will be carried on throughout the coming year. Extension to other species is planned.

Analysis of NIH Program Activities

Budget Data Sheet

NINDB

10. L-15
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$4,500	1		1	0.5		0.5	
FY 1956	5,000	1		1	0.7		0.7	

12. BUDGET ACTIVITY: Research

13. No co-operating units

14.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Neurocytology 4. 5. NINDB L-16

6. Distribution of water and of amino acids in the nervous system

7. Lloyd Guth

8.

9. PROJECT DESCRIPTION.

Objectives: To determine the functional significance of the fact that gamma-aminobutyric acid in mammals is found only in the central nervous system.

Methods employed: Free and protein-bound amino acid extracts from nervous tissue are taken from animals subjected to various experimental conditions, such as dehydration, degeneration of central nervous tissue, regeneration of central nervous tissue. These extracts are studied by the techniques of two dimensional paper chromotography. Water content of these same tissues is studied by means of the Karl Fisher technique. Changes in water content form a base line for evaluation of changes in other constituents.

Major findings: No report as yet.

Significance: This project will provide one step toward furthering our knowledge of the relationship between cytological and biochemical phenomena in the central nervous system. It is possible that it will add to our knowledge of the fundamental phenomena in central nervous system regeneration.

Proposed course of project: This project will be continued and extended along the lines mentioned above during the coming year.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB
L-16
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$4,500	1		1	0.5		0.5	
FY 1956	5,000	1		1	0.7		0.7	

12. BUDGET ACTIVITY: Research

13. No co-operating units

14.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Neurocytology 4. _____ 5. NINDB L-17

6. Quantitative microbiochemical studies of nervous tissue

7. R. Wayne Albers

8. _____

9. PROJECT DESCRIPTION.

Objectives: To characterize the normal biochemical make-up of tissues from certain parts of the nervous system, notably hypothalamus, optic tract and spinal cord; to study the effects of imposing experimental conditions upon these parts of the central nervous system; to follow these patterns in embryological development.

Methods employed: The principle methods are those of Linderstrom-Lang and of Lowry, which employ frozen dried fresh unembedded tissues and permit cytological isolation of cells or portion of cells for microbiochemical analysis.

Major findings: No report as yet.

Significance: This project should contribute basic knowledge in cytobiochemistry of the nervous system. The field is very new and largely unexplored.

Proposed course of project: To embark upon a long term study along the lines outlined above. To co-ordinate findings with future electron microscopical observations.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

NINDB
10. L-17
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$4,500	1	-	1	0.5	-	0.5	
FY 1956	$5,000	1	-	1	0.7	-	0.7	

12. BUDGET ACTIVITY: Research

13. No co-operating units.

14.

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Neurocytology 4. _____ 5. NINDB L-18

6. Electrophoretic patterns of tissue removed from various parts of the central nervous system

7. R. Wayne Albers

8. Milton W. Brightman

9. PROJECT DESCRIPTION.

Objectives: To develop paper electrophoresis as a method complimentary to that outlined in the project on quantitative microbiochemical studies of nervous tissue (NINDB).

Method employed: Paper electrophoresis and related techniques.

Major findings: A wide variety of methods have been adapted for the identification on paper of constituents of the central nervous system. Pilot studies have been carried out concerned with solubilizing certain protein constituents of the central nervous system.

Significance: This project should contribute basic knowledge in cytobiochemistry of the nervous system. The field is very new and largely unexplored.

Proposed course of project: To embark upon a long term study along the lines outlined above. To co-ordinate findings with future electron microscopical observations.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB
L-18
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$5,000	1	-	1	1.0	-	1.0	
FY 1956	$5,000	1	-	1	1.0	-	1.0	

12. BUDGET ACTIVITY: Research

13. No co-operating units.

14.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Neurocytology 4. _____ 5. NINDB L-19

6. Development of new micro methods for determining pyridine nucleotide dependent enzymes in biological material

7. R. Wayne Albers

8. _____

9. PROJECT DESCRIPTION.

Objective: To simplify procedures and make possible simultaneous analysis of large numbers of samples.

Methods employed: It has been found that as many as 50 samples can be incubated at one time and the reaction of the enzymes stopped by adding methyl cellosolve to each sample. After the samples have been sufficiently centrifuged to remove the precipitated protein, the reduced pyridine nucleotide may be measured at leisure by determining the optical density at 340 millimicrons.

Major findings: This method has been found applicable to two different triphosphopyridine nucleotide requiring enzymes, namely 6-phosphogluconic dehydrogenase and glucose-6-phosphate dehydrogenase.

Significance: These methods will be used to extend the project on quantitative microbiochemistry of the nervous system.

Proposed course of project: It is proposed to extend this technique to other enzymes than those which have as yet been explored.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

NINDB

10. L-19
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$4,500	1		1	0.5		0.5	
FY 1956	5,000	1		1	1.0		1.0	

12. BUDGET ACTIVITY: Research

13. No co-operating units

14.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Experimental Neuropathology 4. _____ 5. NINDB L-20

6. Hemodynamic factors concerned with the formation of cerebral hemorrhages

7. Jan Cammermeyer

8. _____

9. PROJECT DESCRIPTION.

Objectives: To determine the ways in which petechial hemorrhages occur in cerebral tissue.

Methods employed: Appropriate physiological devices inserted in arteries and veins permit the continuous recording of blood flow and blood pressure. Experiments are carried out in dogs and monkeys subjected to alterations in cerebral hemodynamics (heart arrest, infarction of brain tissue, anoxia, trauma).

Major findings: This project represents continuation of microscopical studies on human pathological material carried out by the principal investigator prior to joining the Laboratory. The petechial hemorrhages showed anatomical changes indicative of recent development and related to hemodynamic disturbances at the moment of heart arrest.

Significance: Results of the study should provide fundamental information to help us understand the mechanism of cerebral hemorrhages in man, and the significance of their occurrence.

Proposed course of project: Continuation and extension along the lines mentioned above.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

NINDB

10. L-20
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions			Man Years			Patient Days
		Prof	Other	Total	Prof	Other	Total	
FY 1955	$7,600	1	5	6	0.3	0.8	1.1	
FY 1956	$8,300	1	5	6	0.3	0.9	1.2	

12. BUDGET ACTIVITY: Research

13. No co-operating units.

14.

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Experimental Neuropathology 4. _____ 5. NINDB L-21

6. Histochemical characteristics of the brain and spinal cord affected by anesthetics.

7. Jan Cammermeyer

8. _____

9. PROJECT DESCRIPTION.

Objectives: To determine the sequence of histochemical changes that may occur in nerve cells and neuropil in different parts of the central nervous system during and following administration of such anesthetic agents as barbiturates and ether. To discern the rate of recovery of these cells from the effects mentioned.

Methods employed: In cats, dogs, and other species, anesthetics are administered at various doses and length of time to induce nerve cell changes of different intensity. Histochemical analysis involves the use of a number of recently developed techniques.

Major findings: No report as yet.

Significance: The usual histological techniques have been inadequate to determine whether or not and how nerve cells may be altered structurally and chemically by anesthetic agents. More refined methods should provide answers that may be useful in other fields of experimental work and human neuropathology (e.g., sudden anesthesia death).

Proposed course of project: To develop the histochemical techniques with proper control material.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

NINDB

10. L-21
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions			Man Years			Patient Days
		Prof	Other	Total	Prof	Other	Total	
FY 1955	$7,600	1	5	6	0.3	0.8	1.1	
FY 1956	$8,300	1	5	6	0.3	0.9	1.2	

12. BUDGET ACTIVITY: Research

13. No co-operating units.

14.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Experimental Neuropathology 4. _____ 5. NINDB L-22

6. Volumetric studies on the mammalian spinal cord

7. Jan Cammermeyer

8. Junior personnel

9. PROJECT DESCRIPTION.

Objectives: To determine physical and anatomical properties of the spinal cord that support blood flow and prevent development of edema in different normal animals.

Methods employed: The animals used are cat, rabbit, opossum and man. Spinal cord volume before and after exposure to water and salt solutions is determined by a newly devised technique which permits direct reading of volume, segment by segment, in the spinal cord.

Major findings: In a manner characteristic of each species: (A) the spinal cord shows considerable capacity to swell, (B) one region swells more than the others, and (C) the spinal cord coverings resist to increased tension within the cord, as in man, or they yield to it with ruptures, as in opossum and rabbit.

Significance: The research will contribute to understanding the pathogenesis of myelopathies and certain aspects of spinal cord symptomatology.

Proposed course of project: Continue the study with (1) observations on other species (dog, sheep, monkey, etc), (2) histological survey of the material, (3) comparison of the obtained results with those of planigraphic measurements, and (4) to apply the same techniques to animals subjected to trauma, compression ischemia, aortic occlusion ischemia of the spinal cord, forced activity in tread mill, changes in dietary regimen, etc.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

NINDB

10. L-22
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$7,600	1	5	6	0.3	0.8	1.1	
FY 1956	$8,300	1	5	6	0.3	0.9	1.2	

12. BUDGET ACTIVITY: Research

13. No co-operating units.

14.

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Experimental Neuropathology 4. _____ 5. NINDB L-23

6. Hematological and vascular factors in cerebral siderosis

7. Jan Cammermeyer

8. _____

9. PROJECT DESCRIPTION.

Objectives: To determine possible sources of siderosis in the brain, other than from destruction of blood hemoglobin.

Methods employed: Up to the present time histological methods were applied to material from human sources. As a supplementary study, serum iron levels will be determined in animals (rabbit, cat, dog), after which the animals will be subjected to experimental trauma, embolization and anoxia; following another serum iron determination the animals will be sacrificed and the tissues of the brain will be prepared for histological and cytochemical studies.

Major findings: In man, cerebral siderosis manifested itself perivascularly and occurred in subjects in whom there was a decreased ability to incorporate the circulating iron in a stable plasma protein compound. The iron was lost at the site of high vascular permeability.

Significance: The results of this study will aid in evaluating the significance of iron in the brain, i.e., the timing of hemorrhages in the human brain.

Proposed course of project: The animal studies will continue through the coming year.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

NINDB

10. L-23
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$7,600	1	5	6	0.3	0.8	1.1	
FY 1956	$8,250	1	5	6	0.3	0.8	1.1	

12. BUDGET ACTIVITY: Research

13. No co-operating units.

14.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Experimental Neuropathology 4. _____ 5. NINDB L-24

6. Comparative anatomical study of the area postrema of the brain

7. Jan Cammermeyer

8. Junior personnel

9. PROJECT DESCRIPTION.

Objectives: To discover the nature and function of certain cells which are peculiar to the area postrema of the brain.

Methods employed: Conventional cytological techniques are used to study this region in several species of animals.

Major findings: Its relative size and extent over the floor of the fourth ventricle varies greatly (the area postrema of the squirrel is remarkably large). Species differences were noted in certain histochemical qualities of the area postrema. The principal cells have the same structural appearance in all species studied but it is noteworthy that in man they differ from those in all other animals studied, inasmuch as they contain a melaninlike pigment.

Significance: Results of this research should contribute to our knowledge of the control of blood flow through the vasculature of the medulla oblongata (through a possible neurosecretory function of the area postrema cells) and of the formation of thecerebrospinal fluid (through diffusion of substances from the vessels of the area postrema).

Proposed course of project: To continue along the lines mentioned above, adding a number of additional species to the series. Subsequently certain experimental studies will be carried out, involving surgical ablation, injection of substances acting on these areas, histochemical studies, etc.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

NINDB

10. L-24
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$7,600	1	5	6	0.3	0.8	1.1	
FY 1956	$8,250	1	5	6	0.3	0.8	1.1	

12. BUDGET ACTIVITY: Research

13. No co-operating units

14.

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Functional Neuroanatomy 4. _____ 5. NINDB L-25

6. The role of the hypothalamus and other parts of the brain on temperature regulation

7. Leo C. Massopust, Jr.

8. _____

9. PROJECT DESCRIPTION.

Objectives: To determine the effects of placing lesions in various areas of the brain on temperature regulation and on metabolism.

Methods employed: Experimental surgical ablation procedures are used in rats and other animals; other lesions are placed with the Horsley-Clarke stereotaxic instrument, destroying certain discrete centers. Body skin and internal temperatures are taken, oxygen consumption is recorded and the course of nerve pathways will be traced histologically by degeneration techniques.

Major findings: The project is a continuation of one begun at the University of Colorado. Impairment of ability to maintain body temperature followed bilateral destruction of certain areas of the anterior tuberal, and posterior hypothalamus. From this a vital area has been described. Lesions in certain areas of the hypothalamus also cause alteration in basal oxygen consumption rates, sham rage, lipoid dystrophy and altered estrus cycles.

Significance: The project will provide basic information concerning heat production, heat loss and heat conservation and the mechanism of fever. It will lead to knowledge of the location of temperature regulation pathways.

Proposed course of project: Continuation of the study outlined above. The instrument shop is in the process of constructing a stereotaxic instrument to be used for this and other studies in temperature regulation.

Analysis of NIH Program Activities

Budget Data Sheet

NINDB

10. L-25
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$3,570	1	3	4	0.1	0.2	0.3	
FY 1956	$5,000	1	3	4	0.2	0.4	0.6	

12. BUDGET ACTIVITY: Research

13. No co-operating units

14.

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Functional Neuroanatomy 4. _____ 5. NINDB L-26

6. Role of the spinal cord in mechanisms of temperature regulation

7. Leo C. Massopust, Jr.

8. _____

9. PROJECT DESCRIPTION.

Objectives: To determine the pathways in temperature regulation, how the autonomic afferent and efferent pathways in the spinal cord affect temperature regulation and the type of receptor or receptors activating the temperature regulation mechanisms.

Methods employed: Selective interruption of fiber tracts in the spinal cord either by experimental surgical means or by placement of lesions with the Horsley-Clarke stereotaxic instrument; and tracing these pathways in the brain by means of physiological techniques, determination of the effect of these lesions on heat conservation, heat loss and oxygen consumption.

Major findings: This project is a continuation of one begun at the University of Colorado. Pilot experiments indicate that the pathways involved in temperature regulation in the spinal cord are not located in the peripheral areas of the dorsal funiculi. In the rat spinal cord, total transection completely destroyed the temperature regulatory ability. Partial transection of the ventrolateral funiculi did not destroy the temperature regulatory ability of these animals. Recent studies indicate that these pathways may be located in the lateral funiculi or near the cortico-spinal tracts in the central regions of the dorsal funiculi.

Significance: The project will provide additional basic information to a better understanding of the mechanisms involved in fever, and how warm blooded animals protect themselves against over heating and cooling.

Proposed course of project: To subject these animals to various types of stress, particularly heat and cold stress, to determine the efficiency of the various thermoregulatory mechanisms.

Analysis of NIH Program Activities

Budget Data Sheet

NINDB

10. L-26
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$3,570	1	3	4	0.1	0.2	0.3	
FY 1956	$5,000	1	3	4	0.2	0.4	0.6	

12. BUDGET ACTIVITY: Research

13. No co-operating units.

14.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Functional Neuroanatomy 4. _____ 5. NINDB L-27

6. Pyrogenic and antipyrogenic agents in temperature regulation

7. Leo C. Massopust, Jr.

8. _____

9. PROJECT DESCRIPTION.

Objectives: A. To determine the effects of vasodilator, vasoconstrictor pyrogenic and nonpyrogenic drugs on temperature regulations. B. To determine the effect of the temperature of the blood entering and leaving the hypothalamus in the activation and deactivation of temperature regulating mechanisms.

Method employed: By means of physiological techniques, study the effect of injected drugs on normal animals, animals having altered temperature regulating ability and animals with altered body metabolism. Parabiotic studies will be performed on animals with altered temperature regulatory ability.

Major findings: Administration of various derivatives of the ergot alkaloids, both the vasoconstrictors and vasodilators, have shown that, if vasoconstriction is blocked under cold stress, the animal will eventually lose its ability to maintain its body temperature. The reverse is true when vasodilators are used, and the animal is subjected to heat stress; the animal will eventually die from overheating.

Significance: The project will provide basic information concerning heat production, the activation of temperature control mechanisms and the mechanism of fever.

Proposed course of project: It is planned to add increased numbers of animals, to use different drugs (morphine, chlorpromazine, aspirin, etc.) and to study the effects of lesions in the brain on the results obtained. Parabiotic studies, using tubes inserted into the circulation, will be used to alter the temperature of the blood entering the brain; physiological studies will be made on such animals; tracts will be traced.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

NINDB

10. L-27
Serial No.

11. BUDGET ACTIVITY:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$3,570	1	3	4	0.1	0.2	0.3	
FY 1956	$4,900	1	3	4	0.2	0.3	0.5	

12. BUDGET ACTIVITY: Research

13. No co-operating units.

14.

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Functional Neuroanatomy 4. _____ 5. NINDB L-28

6. The efferent or recurrent fibers of the central and peripheral auditory pathways in mammals

7. Grant L. Rasmussen

8. _____

9. PROJECT DESCRIPTION.

Objectives: To trace the course and establish the connections of chains of neurons from the cerebral cortex to the cochlea.

Methods: Placement of lesions surgically in cats and monkeys, subsequently following intrinsic degeneration of axons and their terminations by means of Swank-Davenport, Nauta, and methylene blue techniques.

Major findings: This project is a continuation of a study carried out by the responsible investigator at the University of Buffalo School of Medicine, sponsored there by ONR. It has revealed indications of an orderly system of connecting neurons conducting impulses from the auditory cortex to the cochlea, or organ of hearing.

Significance: Establishment of the presence of efferent fibers in a sensory nerve, such as that of hearing, is a new discovery. This system evidently represents an auditory "feed-back" mechanism. Electrophysiological studies, being carried on in collaboration with Dr. Galambos at Walter Reed Hospital, indicate that these efferent fibers have inhibitory or suppressor effects upon the afferent cochlear nervous activity.

Proposed course of project: Important anatomical details remain to be worked out. Correlations remain to be drawn with electrophysiological studies.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

NINDB
10. L-28
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$3,570	1	3	4	0.1	0.2	0.3	
FY 1956	$5,000	1	3	4	0.2	0.3	0.5	

12. BUDGET ACTIVITY: Research

13. Co-operating Units: Dr. Robert Galombos
Walter Reed Medical Center

14.

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Functional Neuroanatomy 4. _____ 5. NINDB L-29

6. Autonomic innervation of the inner ear

7. Grant L. Rasmussen

8. _____

9. PROJECT DESCRIPTION.

Objectives: To discover the origin and pathways of the autonomic fibers innervating the inner ear; particularly the sympathetic component.

Methods employed: Methods of experimental surgery in cats followed by degeneration of nerve fibers detected by special neurological techniques. Neurophysiological methods will also be employed.

Major findings: Certain routes postulated by otologists for fibers to reach the inner ear have been explored with, as yet, negative results.

Significance: It is generally assumed that the autonomic system should play an important role in the proper functioning of the hearing and equilibratory organs. The delicate pressure balance between the endolymphatic and perilymphatic fluid systems is maintained in a large measure by the influence of secretory fibers and that vasomotor control is presumably mediated by sympathetic nerves. Vasomotor disturbance of the labyrinth arteries is thought by many otologists to be responsible for tinnitus and equilibratory disturbances and that unequal pressures of the endo- and perilymph results in a condition known as "hydrops". This causes hearing and equilibratory disturbances (Menière's disease). The design of critical physiological experiments for testing the functional role of the autonomic nerves is dependent on knowledge of the precise origin, course and termination of nervous components involved.

Proposed course of project: Continuation of this study with exploration of the other possible routes. Extension of study to monkeys.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

NINDB

10. L-29
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$3,570	1	3	4	0.1	0.2	0.3	
FY 1956	$5,000	1	3	4	0.2	0.4	0.6	

12. Budget Activity: Research

13. No co-operating units.

14.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Functional Neuroanatomy 4. _____ 5. NINDB L-30

6. The precise termination of certain descending intraspinal fiber tracts

7. Grant L. Rasmussen

8. _____

9. PROJECT DESCRIPTION.

Objectives : To determine precisely upon what cell groups the descending fibers of tracts in the spinal cord terminate.

Methods employed: Production of lesions surgically at appropriate places in the central nervous system of monkeys and cats, following the course of degeneration by means of the Nauta technique and other neurological techniques which demonstrate degeneration of the axon terminals.

Major findings: Preliminary work has been confined to development of adequate techniques.

Significance: Knowledge of the precise termination of the principal descending fiber tracts in the brain stem and spinal cord is almost completely lacking. The research aims to provide such knowledge which is basic to understanding neurological disorders.

Proposed course of project: To continue this project and expand it during the course of the coming year.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

NINDB

10. L-30
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$3,570	1	3	4	0.1	0.2	0.3	
FY 1956	$5,000	1	3	4	0.2	0.4	0.6	

12. BUDGET ACTIVITY; Research

13. No co-operating units.

14.

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB 2. Laboratory of Neuroanatomical Sciences

3. Section on Functional Neuroanatomy 4. _____ 5. NINDB L-31

6. Origin and termination of the frontopontine tract

7. Grant L. Rasmussen

8. _____

9. PROJECT DESCRIPTION.

Objectives: A. To determine whether or not the frontopontine tract possesses fibers of subcortical origin. B. To trace fiber components to termination in pons.

Methods employed: Performance of total and subtotal hemispherectomies in monkeys and other species of animals; placement of lesions in cerebral peduncle; determination of the origin, course and endings of the fibers by means of suitable neuropathological techniques.

Major findings: Preliminary studies in material taken from human hemispherectomy cases suggest a possible subcortical origin of numerous thinly myelinated fibers of this tract. No results have accrued as yet from animal experiments.

Significance: Observations resulting from this project should (a) add to our knowledge regarding the origin and termination of this tract; (b) form a basis for subsequent physiological studies of its function and (c) lead to an understanding of the results obtained in humans after section of the frontopontine tract as is practiced in certain neurological procedures.

Proposed course of project: To continue and extend this study particularly on primates and additional human hemispherectomy cases that might be obtained throughout the coming year. It should be noted that other fiber tracts connecting the cerebral cortex and lower centers will be investigated by similar methods as time, personnel and facilities permit.

R.P.C. -2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB
L-31
Serial No.

11. BUDGET DATA:

	Estimated Expenditures	Budgeted Positions Prof	Other	Total	Man Years Prof	Other	Total	Patient Days
FY 1955	$3,580	1	3	4	0.1	0.3	0.4	
FY 1956	$5,000	1	3	4	0.2	0.4	0.6	

12. BUDGET ACTIVITY: Research

13. No co-operating units.

14.

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness 2. Laboratory of Neurophysiology

3. Spinal Cord 4. 5. NINDB L-32
SERIAL NO.

6. Dorsal Root Potential Measurements

7. M.G.F. Fuortes and K. Frank

8. Mary Becker, I. Tasaki

9. Objectives: The objective of this project was to determine the origin of the slowly changing potentials appearing on the dorsal roots of the spinal cord following a sudden stimulation of these nerves.

Methods employed: To determine this, the slow potential has been observed in response to single and multiple shocks to the same and neighboring dorsal roots and to shocks delivered through microelectrodes in the spinal cord. The variations observed in the slow potential in response to these stimuli permit certain conclusions regarding their origin.

Major findings: While the approach taken in this project has not led to a satisfactory explanation for the origin of dorsal root potentials, findings to date do indicate that they cannot be due to direct electrical interaction between fibers (a currently popular view) nor can their origin be inferred from the relative signs of potentials on adjacent roots. The finding that very similar potentials arise when microelectrodes are used to stimulate only postsynaptic nerve cells implies a postsynaptic origin. But failure to record significant slow potentials with intrafiber microelectrodes casts doubt even on the currently accepted mechanism of cable-like conduction of these slow potentials.

Significance to Neurology Research: While the objective of this project is the resolution of an extremely technical point, it is of some importance in the field of neurophysiology. Different origins and different roles have been ascribed to the dorsal root potential in the literature. It is thought by some to be the cause of "the central excitatory state". Such possible mechanisms must be either demonstrated or disproved.

Proposed course of project: The findings from this project, began in 1953 and continued through calendar year 1954, have been written up for publication and presented at the Atlantic City Meetings of the American Federation of Biological Sciences. The paper has not been submitted for publication pending a more detailed analysis of the mechanism of conduction of dorsal root potentials. The project therefore is temporarily interrupted until this and new methods of attack can be devised.

Budget Data Sheet

10. NINDB L-32
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS		
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL
FY 1955	$4,748.00	1	1	2	1/3	1/3	2/3

12. Research

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 10).

This was a cooperative project carried out with Dr. M.G.F. Fuortes of the research staff of the Army Medical Center at Walter Reed Hospital as senior investigator. Work was performed at both laboratories but there was no exchange of funds.

14. None

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness 2. Laboratory of Neurophysiology

3. Spinal Cord Section 4. 5. NINDB L-33
SERIAL NO.

6. Origin of rhythmic activity in the spinal cord

7. K. Frank

8. M. Becker [illegible]

9. Objectives: This project has as its major goal the determination of the origin of the rhythm of trains of impulses recorded from single nerve cells in the spinal cord. Specifically, it is desired to know whether the pacemaker for a train of nerve impulses coming from a single cell lies in that cell or outside it.

Methods employed: Intracellular microelectrodes are used to stimulate or record from single nerve cells in the spinal cord of cats. Direct stimulation of such cells can, by its affect on their rhythmic activity, determine the locus of the pacemaker for that rhythm.

Major findings: The significant major finding to date is that at least some of the motor horn cells of the lumbosacral cord do generate their own rhythms.

Significance to Neurology Research: The ability of individual nerve cells in the central nervous system to generate their own rhythmic trains of impulses has frequently been suggested but alternative mechanisms have also been proposed. To demonstrate the existence of this type of behavior is therefore a step forward in understanding how the nervous system operates. It is inevitable that from a detailed knowledge of the normal behavior of the nervous system will come the systematic advances in dealing with its diseases.

Proposed course of project: The studies by this method have so far been restricted to motoneurons, those spinal cord cells whose axons are available for stimulation outside the cord. By stimulating through the same electrode used for recording, it is hoped to extend the method to cells lying totally within the cord. For those cells which do not generate their own rhythms, a variation of this method makes it possible to determine whether various nervous pathways include the pacemaker for the cell penetrated. The results of such measurements should add materially to an understanding of the origins of rhythmic activity in the spinal cord.

Honors, Awards, and Publication Sheet

15. NINDB L-33
SERIAL NO.

16. None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Findings from this project were presented at the Neurophysiology Group Meeting of the American Physiological Society in Madison, Wisconsin by invitation.

R. P. C. - 2
December 1954 Analysis of NIH Program Activities

Budget Data Sheet
Project Description Sheet

10. NINDB L-33
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS		
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL
FY 1955	$6,748.34	1	2	3	1/3	2/3	1
FY 1956	$9,616.37	2	3	5	2/3	1	1-2/3

12. BUDGET ACTIVITY:

Research

13. None

14. None

Project Description Sheet

1. Neurological Diseases and Blindness 2. Laboratory of Neurophysiology

3. Spinal Cord Section 4. 5. NINDB L-34
SERIAL NO.

6. Mechanisms of interaction between neurons in the spinal cord

7. K. Frank, M.G.F. Fuortes, R. Morrell

8. M. Becker

9. Objectives: The broad objectives of this, the main project of the Spinal Cord Section, are the investigation of basic mechanisms of neuronal interaction of the central nervous system operating in the spinal cord.

Methods employed: The principal tool used in these investigations is the salt-filled ultramicroelectrode. Electrodes of this type are placed inside single nerve cells or fibers in the spinal cord and are used to record the electrical signs of nervous activity, either spontaneous or in response to various stimuli applied to the peripheral nervous system or to the penetrated cell directly through the recording electrode.

Major findings: Significant findings are: 1. When a motor horn cell is caused to fire repetitively by physiological stimuli there is no apparent sudden synaptic potential preceding each impulse while with synchronous electrical stimulation of large nerves or roots such prespike potentials are often seen. 2. During repetitive firing of some cells a "saw-tooth" like potential is seen suggesting that depolarization of the cell membrane leading to excitation is destroyed when the cell fires and is only gradually rebuilt. But it has not been determined whether this is a normal or abnormal form of cell behavior. 3. Trains of shocks delivered to various peripheral paths have been shown to produce trains of impulses in some interneurons but at a different frequency of firing. 4. Single interneurons have been found which respond to a wide variety of peripheral stimuli. These have been named "alerting cells" because of the possibility that they serve such a function in the normal animal, perhaps reducing escape-reaction-time by lowering certain motoneuron thresholds. 5. Other interneurons have been shown to respond to peripheral stimuli with frequency modulated trains of impulses. It is considered possible that the character of the frequency modulation contains "information" regarding the nature of route of the excitation reaching the interneuron. 6. The slow wave and spike trains seen with strychnine tetanus have been shown to occur in interneurons

as well as motoneurons. 7. An increase in membrane potential of a motoneuron has been seen following stimulation but this was not associated with inhibition as reported in the literature.

Significance to Neurology Research: These findings provide basic information regarding the types of interactions occurring between neurons and therefore add to the understanding of the behavior of the central nervous system. The application of such information to the treatment of diseases of the nervous system is a real hope for the distant future.

Proposed course of project: The proposed course of this project is a continuation of the aspects of neuronal interaction described above. The emphasis will be on patterns of responses to reasonably physiological stimuli in contrast to massive, synchronous, electrical stimuli. Aspects which appear particularly promising are effects of bridge stimulation of the penetrated cell through the microelectrode, patterns of interaction between upper and lower spinal cord, and the responses of single cells to modification of their local chemical environment through the use of concentric micropipettes.

 Analysis of Program Activities

Budget Data Sheet

10. NINDB L-34
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS		
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL
FY 1955 NINDB	$8,385.00	1	3	4	1/3	1	1-1/3
NIMH	1,000.00	0	1	1	0	1/3	1/3
TOTAL	$9,385.00	1	4	5	1/3	1-1/3	1-2/3
FY 1956 NINDB	$15,708.00	2	4	6	1-1/3	1-1/3	2-2/3
NIMH	1,000.00	0	1	1	0	1/3	1/3
TOTAL	$16,708.00	2	5	7	1-1/3	1-2/3	3

12. BUDGET ACTIVITY:

Research

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 10)

This is a cooperative project carried out in part with Dr. M.G.F. Fuortes of the research staff of the Army Medical School at Walter Reed Hospital.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

Three research projects within the PHS use similar methods to study behavior of single neuronal elements in the cortex or peripheral nervous system. They are:

a. Dr. Ichiji Tasaki SERIAL NO. NINDB L-36

b. Dr. Walter Freygang, Jr. SERIAL NO. NIMH-6

c. Dr. Choh-Luh Li SERIAL NO. NINDB-33(C)

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness 2. Laboratory of Neurophysiology

3. Spinal Cord 4. 5. NINDB L-35
SERIAL NO.

6. Laboratory Course in Neurophysiology

7. K. Frank, M.G.F. Fuortes

8.

9. Objective: The purpose of this course is to teach a few of the junior members of the laboratory some practical aspects of neurophysiology, to stimulate their interest and to enable them to participate more fully in the problems on which they are working.

Proposed course of project: It is proposed to begin this course in February 1955 on a one evening per week schedule to be continued indefinitely. While there will be no official time devoted to this project it is planned to use laboratory facilities and a few laboratory supplies.

Budget Data Sheet

10. NINDB L-35
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS		
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL
FY 1955	$100.00						
FY 1956	$200.00						

12. Research

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 10)

Dr. M.G.F. Fuortes of the research staff of the Army Medical School at Walter Reed Hospital is giving the course jointly with Dr. K. Frank.

14. None

R.P.C. -1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness 2. Laboratory of Neurophysiology

3. Section on Special Senses 4. 5. NINDB L-36
SERIAL NO.

6. Experimental studies on the process of initiation of nerve impulses

7. Dr. I. Tasaki

8. Dr. C. Spyropoulos

9. Objectives: The objective of this project is to find out the conditions under which nerve impulses are initiated in the nerve fiber.

Methods Employed: With a high input impedance amplifier (recently developed for recording action potentials with microelectrodes), it has been found possible to record the membrane potential at the node of Ranvier in isolated myelinated nerve fibers faithfully. By observing these membrane potentials the process of initiation of an impulse in the myelinated nerve fiber has been analyzed.

Major findings: The major finding of this project during the past year has been: 1) the development of the method of recording the membrane potential described above (Tasaki and Frank), 2) measurements of the physical constants of the frog nerve fiber by using the data obtained by the new method (Tasaki), 3) demonstration of the parallelism between the action potential, action current and the membrane impedance during activity (Tasaki and Freygang) and, 4) demonstration of abolition of an action potential by anodal current pulses (Tasaki).

Significance to Neurology Research. 1) the finding by Tasaki and Frank indicates that the absolute value of the action potential in the frog nerve fiber is between 97 and 110 millivolts and that the electric current (local circuit theory) plays a decisive role in initiation and propagation of the nerve impulse, 2) the determination of the physical constants of the nerve fiber is essential for an analytical consideration of the process of excitation and conduction in the nerve fiber, and it has also clarified the effects of some drugs and of temperature changes upon the nerve fiber, 3) demonstration of the parallelism between the three measurable electric signs of activity of the nerve fiber has an important bearing on the generally accepted theory of nerve excitation, 4) the demonstration that an action potential can be abolished after it has once been initiated

reveals the presence of two stable states in the nerve membrane and also clarifies the significance of the refractoriness of the nerve fiber. Only by establishing a firm foundation of factual understanding of the physiology of the normal nervous system, advances can be made in the treatment of abnormal conditions.

Proposed course of project: Analysis of the process of accommodation in the myelinated nerve fiber and studies of the effects of various chemicals upon the fiber are now in progress. The results obtained so far appear to shed some light on the problem of sensory adaptation.

In the period between June and July 1955, research work at Marine Biological Laboratory at Woods Hole, Massachusetts is planned. The purpose is to compare invertebrate nerve fibers with the frog myelinated fiber and to see if the sodium-theory of nerve excitation (Hodgkin and Huxley) proposed for the squid giant axon is applicable to vertebrate myelinated fibers.

After August 1955, the main research activity under this project will be directed toward analysis of the effects of various enzyme inhibitors upon the process of initiation of nerve impulses.

 Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB L-36
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS		
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL
FY 1955 NIMH	$ 1,700.00		2	2		2/3	2/3
NINDB	$12,000.00	2	2	4	2	1-2/3	3-2/3
TOTAL	$13,700.00	2	4	6	2	2-1/3	4-1/3
FY 1956 NIMH	$ 1,000.00		1	1		1/3	1/3
NINDB	$11,800.00	2	3	5	1	2	3
TOTAL	$12,800.00	2	4	6	1	2-1/3	3-1/3

12. BUDGET ACTIVITY:

Research

13. None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

Dr. K. S. Cole - Project on nerve membrane and action potentials.

Dr. A. Shanes - Project on effects of ions and drugs on nerve action potentials.

R.P.C. -1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness 2. Laboratory of Neurophysiology

3. Section on Special Senses 4. 5. NINDB L-37 SERIAL NO.

6. Analysis of the sensory mechanism in the inner ear.

7. I. Tasaki, S. Spyropoulos and L. N. Tasaki

8. None

9. Objectives: The objective of this project is to clarify the mechanism by which nerve impulses are initiated in the auditory nerve fibers in response to acoustic stimulation.

Method employed: The cochlea of an anaesthetized guinea pig is exposed and small holes are drilled through its bony wall. Micropipettes for recording the cochlear potentials and for injection of various chemicals are introduced into the endo- and perilymphatic spaces. The changes in the cochlear potentials (nerve, microphonic and d.c. potentials) are analyzed to clarify the auditory mechanism. Preliminary experiments were done in collaboration with Dr. H. Davis during 3 weeks visit at the Central Institute for the Deaf, St. Louis, Mo.

Major findings: It has been shown possible in the preliminary experiments to record microphonic and d.c. potentials directly from inside the endolymphatic space. It was also found possible to inject chemicals into the endolymphatic space and to study the changes in the cochlear potentials.

Significance to Neurological Research: It has been shown previously (Tasaki, Davis and Eldridge, J. Acous. Soc. Amer. September 1954) that the variation in the large potential drop across the hair-bearing end of the hair-cells is the first physiological process caused by acoustic stimuli applied to the cochlea. Further analysis of this large hair-cell potential is expected to lead us to a better understanding of the process of normal hearing and of the cause of certain types of deafness.

Proposed course of project: Azide, cyanide and anoxia have been shown to reduce the cochlear potentials reversibly. The effects of injection of other enzyme poisons, and of variations in the pH in the endolymph will be investigated.

R.P.C. - 2
December 1954 Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB L-37
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS		
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL
FY 1955	$ 664.00	1	1	2	1/12	1/12	1/6
FY 1956	$1200.00	1	1	2	1/4	1/4	1/2

12. BUDGET ACTIVITY:

Research

13. None

14. None

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness 2. Laboratory of Neurophysiology

3. Section on Special Senses 4. 5. NINDB L-38
SERIAL NO.

6. Analysis of the nerve impulses arising in the retina

7. Dr. I. Tasaki

8. None

9. Objectives: The purpose of this project is to develop methods of recording afferent nerve impulses in individual nerve cells and nerve fibers in the retina and to elucidate the physiological basis of color vision.

Methods employed: See proposed course.

Major findings: Construction of special equipment required for this project is under way. Experiments on biological material are scheduled to begin about February or March 1955.

Significance to Neurology Research: To understand how the eye functions, it is desirable to obtain information concerning the responses of the individual sensory elements in the retina to various kinds of light stimuli. At present, there is very little known about the mechanism of color vision in the bird and in primates.

Proposed course of project: In the preliminary experiments it is planned to work on the eye of the bird (either pigeon or chicken). The eye will be exposed to a sequence of light stimuli of different colors. A hyperfine microelectrode for recording nerve impulses will be introduced into the optic nerve (or into the retina) while the light stimuli are being applied to the eye of the animal. It is hoped that the electrical response to be recorded from these electrodes will reveal basic aspects of the mechanism of color vision.

Budget Data Sheet

10. NINDB L-38
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS		
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL
FY 1955	$10,100.00	1	1	2	1/2	1/2	1
FY 1956	$ 6,800.00	1	1	2	1/2	1/2	1

12. BUDGET ACTIVITY:

Research

13. None

14. None

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness 2. Laboratory of Neurophysiology

3. Section on Special Senses 4. Marine Biological Lab. Woods Hole, Mass. 5. NINDB L-39 SERIAL NO.

6. Simultaneous measurement of impedance and action potential recorded from an intra-cellular electrode in the squid giant axon

7. I. Tasaki and W. H. Freygang, Jr.

8. None

9. Objectives: To further define the relationship between the nerve impulse and the permeability changes of the active neural membrane.

Method employed: Two glass capillary micropipettes are to be inserted in the squid's giant axon. One of these micropipettes will supply an alternating current and a record of the voltage across the membrane will be obtained from the other micropipette.

Significance to Neurology Research: The temporal relationship between the action potential and the associated permeability change will provide a basis for the evaluation of current hypothesis which describe the mechanism of production of the nerve impulse. The data from the frog nerve fiber (see project 'Experimental studies on the process of initiation of nerve impulses') do not agree with the current view of nerve excitation formulated primarily to interpret the data from the squid axon. Therefore, it is imperative to repeat some of the previous experiments on the squid giant axon using our technique.

Budget Data Sheet

10. NINDB L-39
SERIAL NO.

11. BUDGET DATA:

This is covered by project "The effect of Intra-Cellularly injected ions upon the membrane permeability of the squid giant axon" by C. S. Spyropoulos, W. H. Freygang, Jr. and I. Tasaki at Woods Hole, Massachusetts.

12. BUDGET ACTIVITY:

Research

13. None

14. None

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness 2. Laboratory of Neurophysiology

3. Section on Special Senses 4. Marine Biological Lab. Woods Hole, Mass. 5. NINDB L-40 SERIAL NO.

6. The effect of intra-cellularly injected ions upon the membrane permeability of the squid giant axon

7. C. S. Spyropoulos, W. H. Freygang, Jr. and I. Tasaki

8. None

9. Objectives: To evaluate the effects of ionic changes occuring at the inner surface of the axonal membrane

Methods employed: Transverse impedance measurement will be made on the squid axon. External electrodes will supply alternating current and will form one arm of a Wheatstone bridge. Intra-cellular injections will be made into the portion of the axon resting between the electrodes.

If possible, the intra-cellular recording technique of the project on "Simultaneous measurement of impedance and action potential recorded from an intra-cellular electrode in the squid giant axon" will be employed for the impedance measurements.

Significance to Neurology Research: Although the effects of changes in extra-cellularionic concentration have been studied extensively, the effects of intra-cellular changes have been neglected. Existing hypothesis predict the results of this project and the study will provide a new basis for the evaluation of these hypothesis.

 Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB L-40
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS		
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL
FY 1955							
NIMH	$1,875.00	1		1	1/8		1/8
NINDB	2,100.00	2	1	3	1/4	1/8	3/8
TOTAL	$3,975.00	3	1	4	3/8	1/8	1/2
FY 1956							
NIMH	$ 875.00	1		1	1/8		1/8
NINDB	2,300.00	2	1	3	1/4	1/8	3/8
TOTAL	$3,175.00	3	1	4	3/8	1/8	1/2

12. BUDGET ACTIVITY:

Research

13. None

14. None

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Neurological Diseases and Blindness 2. Laboratory of Neurochemistry

3. Section on Lipid Metabolism 4. Bethesda, Md. 5. NINDB L-41 SERIAL NO.

6. Ribose Metabolism

7. Roscoe Brady

8. Bernard Agranoff

9. Project: Elucidation of the pathways of ribose metabolism.

Objectives: The objective of this project is to demonstrate the biochemical mechanisms for the uptake and utilization of ribose by various tissues.

Methods employed: Classical enzymological investigative methods are being employed to determine if tissues can initially activate ribose and subsequently metabolize it in a manner which is presumed to be somewhat similar to the activation of glucose by the enzyme hexokinase.

Major findings: We have demonstrated that viable tissue slices and minced tissue preparations can rapidly remove ribose from the incubation medium. Furthermore, cell free preparations of rat liver appear to be able to metabolize ribose and a preliminary fractionation of the crude system has been accomplished.

Significance to Neurological Diseases Research: The metabolism of ribose may represent another mechanism whereby cells can obtain a source of energy for their viability and function. Furthermore, it appears likely that ribose being a 5-carbon sugar will be broken down into a 2 and a 3 carbon fragment. The nature of the "active" 2-carbon fragment remains to be elucidated, but it is not unlikely that it can participate in the biosynthesis of lipids which constitute an important part of the substance of brain and neural tissue.

Proposed course of project: The immediate problem is to attempt to isolate and characterize the enzyme responsible for the initial step in the metabolism of ribose. It may be tentatively termed a ribokinase since it must of necessity activate the ribose molecule. The nature of the activated product must be established. Preliminary work suggests that it may be a phosphorylated intermediate. The identification and isolation of the active complex will enable further research to be carried out with regard to the subsequent fate of ribose.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB L-41
SERIAL NO.

11.

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS		
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL
F.Y. 1955	17,100	1-1/4	1-1/4	2-1/2	1/2	1	1-1/2
F.Y. 1956	11,900	1	1	2	1	1	2

12. RESEARCH

13. NONE

14. NONE

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Neurochemistry — LABORATORY OR BRANCH
3. Lipid Metabolism — SECTION
4. _____ — LOCATION (IF OTHER THAN BETHESDA)
5. NINDB L-42 — SERIAL NO.

6. Enzymatic thioltransacetylation — PROJECT TITLE

7. Roscoe Brady — PRINCIPAL INVESTIGATOR

8. E. R. Stadtman — OTHER SENIOR INVESTIGATORS

9. PROJECT DESCRIPTION:

Project: To elucidate the enzyme systems present in various tissues which effect the transfer of high-energy thiol (sulfur) esters.

Objectives: The objective of this project is to demonstrate the kinetics and to determine the free energy change which occurs during the transfer of an acyl group from one mercaptan to another.

Methods employed: Analytical methods have been developed which demonstrate the transfer of acyl groups from coenzyme A to other mercaptans. Enzymes have been demonstrated in brain and liver which accomplish this transfer. A particularly active enzyme has been found in the bacterium Clostridium kluyveri and partial purification has been effected.

Major findings: Enzymes in brain, liver, and other tissues have been demonstrate which transfer the acyl group from one thiol ester to another. A study of the substrate specificity of partially purified liver enzymes has been accomplished. Preliminary kinetic studies have also been completed.

Significance to Neurological Diseases Research: The important role of high-energy thiol esters has become increasingly obvious as a result of the work of Lipmann, Nachmansohn, Ochoa, and Lynen. These bonds contain sufficient energy to accomplish many biosynthetic processes such as fatty acid, cholesterol, and acetyl choline synthesis. Furthermore, through various transfer reactions, it is apparent that adenosine triphosphate (ATP)can be formed from certain thiol esters. It is frequently necessary to transfer the acyl groups of a particular thiol ester which may be formed in a biological reaction to another in which form it may be of more general usefulness, e.g., for the synthesis of ATP, etc. Hence, the importance of the existence and knowledge of such enzyme transfer mechanisms becomes immediately apparent.

R.P.C. - 2
December, 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB L-42
SERIAL NO.

11.

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS		
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL
F.Y. 1955	3,200	1/4	1/4	1/2	1/4		1/4
F.Y. 1956	2,800	1/4	1/4	1/2	1/4	1/4	1/2

12. RESEARCH

13. For several weeks during the first half of fiscal year 1955 worked in collaboration with Dr. Earl Stadtman of the Laboratory of Cellular Physiology and Metabolism in the National Heart Institute.

14. NONE

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB L-42
SERIAL NO.

16. Enzymatic Thioltransacetylation, Federation Proceedings, 13, 186, 1954.

Enzymatic Thioltransacetylation, Journal of Biological Chemistry, 211, 621, 1954.

Enzymatic Thioltransacetylation, Recent Progress in Neurochemistry and Allied Sciences, in press.

17. Seminar by invitation, Faculte de Sciences, University of Paris (Sorbonne) April 29, 1954.

Project Description Sheet

NINDB L-42
SERIAL NO.

Proposed course of project: A highly purified enzyme has been obtained from Cl. kluyveri in suitable amounts for kinetic and equilibrium studies. From these data, it is hoped that the free energy change, if any, of this reaction may be calculated and an accurate evaluation of the role of these transfer enzymes in the metabolic economy of the cells may be ascertained. It is hoped that this project will be terminated at the end of fiscal year 1956.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Neurochemistry — LABORATORY OR BRANCH
3. Lipid Metabolism — SECTION
4. — LOCATION (IF OTHER THAN BETHESDA
5. NINDB L-43 — SERIAL NO.

6. Metabolic Activity of Coenzyme A Derivatives
PROJECT TITLE

7. Roscoe Brady
PRINCIPAL INVESTIGATOR

8.
OTHER SENIOR INVESTIGATORS

9. PROJECT DESCRIPTION:

Project: Preparation and investigation of the enzymatic activity of substituted derivatives of acetyl coenzyme A.

Objectives: Fluoroacetic acid has been shown to be a very powerful poison and the mechanism of its toxic action is presumed to be via the formation of fluorocitric acid. In order for fluorocitric acid to be formed, fluoroacetic acid must, as far as is known, be activated and made available to the proper enzymes in the form of the energy rich coenzyme A complex. It is proposed to study the reactivity of fluoroacetyl coenzyme A and other coenzyme A derivatives in order to learn the nature of the toxic action of fluoroacetic acid and further to investigate the nature of enzyme substrate intermediary complexes.

Methods employed: Substituted acetyl coenzyme A derivatives will be prepared by suitable chemical methods. The various enzymes to be studied will be prepared in the form of their highest purity. The reactivity of the complexes with the enzymes will be observed by the respective techniques and methods for the various reactions. The kinetics of these reactions will be calculated and compared with those of authentic samples.of unsubstituted coenzyme A complexes.

Major findings: Fluoroacetyl coenzyme A has been found to be very active in several enzyme systems. It does indeed condense with oxalacetate in the presence of the crystalline condensing enzyme to form fluorocitrate, and furthermore, it appears to be a competitive inhibitor of the natural substrate, acetyl coenzyme A, in this system. In some enzymatic reactions, it actually reacts much faster than does the natural acetyl coenzyme A.

Analysis of NIH Program Activities

Project Description Sheet

NINDB L-43
SERIAL NO.

Significance to Neurological Diseases Research: The importance of high energy coenzyme A derivatives is certainly immediately apparent when one considers that these are the reactive intermediates for the synthesis of fatty acids, cholesterol and other cerebral lipids. It is through the intermediary steps of these complexes that carbohydrate is able to enter the tricarboxylic (citric) acid cycle and hence be burned and the energy of glucose made available to the cell. It is via coenzyme A complexes that acetyl choline is synthesized. A contribution which sheds some light on the mechanism of the reactivity of these extremely important compounds should obviously prove to be exceedingly rewarding.

Proposed course of project: The products of the enzymatic reactions of the substituted coenzyme A derivatives will be identified and characterized. The kinetics and equilibrium data for fluoroacetyl coenzyme A in certain enzymatic reactions will be calculated in order to attempt to learn more about the nature of enzyme - substrate activation in biological processes. Furthermore, it is hoped that more information may be obtained about the nature of the actual high energy bond of coenzyme A complexes.

R.P.C. - 2
December, 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB L-43
SERIAL NO.

11.

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS		
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL
F. Y. 1955	16,800	1-1/4	1-1/4	2-1/2	1/2	1/2	1
F. Y. 1956	15,100	1	1	2	1	1	2

12. RESEARCH

13. NONE

14. NONE

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Neurological Diseases and Blindness 2. Laboratory of Neurochemistry

3. Section on Lipid Metabolism 4. Bethesda, Md. 5. NINDB L-44 SERIAL NO.

6. Biosynthesis of Cerebrosides

7. Roscoe Brady

8. Robert Burton

9. Project: Investigation of the enzymatic pathway of cerebroside synthesis and factors which affect the process.

Objectives: The objective of this project is to discover the biological processes involved in cerebroside synthesis. Since a large portion of brain lipid exists in the form of cerebrosides, and since there are known to be striking abnormalities in cerebroside metabolism in conditions such as Gaucher's disease, it is felt that a demonstration and elucidation of the metabolic pathways of cerebroside synthesis and catabolism would be an important contribution.

Methods employed: Suitable analytical methods for the isolation and characterization of cerebrosides must be developed. When satisfactory procedures have been accomplished, the biosynthesis of cerebrosides will be investigated with the use of carbon-14 labeled galactose since this compound is a known constituent of cerebrosides. Preliminary investigations will be attempted in vivo followed by isolated tissues (particularly brain), and then progressing to the individual enzymatic reactions involved.

Major findings: The project has not yet been undertaken.

Significance to Neurological Diseases Research: Since the major non-aqueous component of brain and nerve tissue is lipid and a large percentage of this lipid is in the form of cerebroside, a knowledge of the pathways of synthesis, storage, breakdown or removal of cerebrosides and the conditionswhich affect these processes would appear to be of great value. It would be of great advantage to learn why in certain conditions there appears an excess or a depletion of these materials, and hence, if possible, to attempt to alter the circumstances responsible for the abnormal condition.

Proposed course of project: It is anticipated that a considerable proportion of the calendar year will be devoted to mastering satisfactory isolation and purification schemes and techniques since many of the analytical details remain to be worked out. Following the successful accomplishment of analytical procedures, the metabolic studies will be undertaken as described under methods.

R.P.C. - 2
December, 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB L-44
SERIAL NO.

11.

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS		
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL
F. Y. 1955	3,000	1/4	1/4	1/2	1/4		1/4
F. Y. 1956	9,900	3/4	3/4	1-1/2	3/4	3/4	1-1/2

12. RESEARCH

13. NONE

14. NONE

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. N.I.N.D.B. — INSTITUTE
2. Laboratory of Biophysics — LABORATORY OR BRANCH — NINDB
3. ___ — SECTION
4. ___ — LOCATION
5. L-45 — SERIAL NO.

6. Ion Permeabilities of Nerve Membranes.
A. Experimental investigations of the squid giant axon.
PROJECT TITLE

7. Moore, J. W.; Cole, K. S.
PRINCIPAL INVESTIGATORS

8. ---
OTHER INVESTIGATORS

9. Project Description:

Objectives: The interpretation of nerve function in terms of fast ionic transports and the elucidation of the structures and mechanisms by which these transports are controlled.

Methods Employed: The measurement of the axon membrane current and potential under controlled electrical, geometrical and ionic conditions from which the individual ionic movements are determined.

Major Findings: None.

Significance to NINDB Research: The recently developed concept and the measurements of the sodium and potassium ion movements across the squid axon membrane offer a new, highly specific and general approach to the factors underlying normal and pathological nervous processes which cannot as yet be investigated directly in higher animals and man.

Proposed Course of Project: The time courses and magnitudes of the sodium and potassium ion currents will be measured in external media containing ionic, organic and biochemical agents that have known or suspected action on nerve performance on the one hand and that represent possible tools for the analysis of the ion transport mechanisms on the other hand.

R.P.C. - 2
December 1954

Budget Data Sheet

10. NINDB L-45
SERIAL NO.

11.
BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	22,700	1-5/6	1-5/6	3-2/3	5/6	1	1-5/6	
FY 1956	25,300	1-5/6	1-5/6	3-2/3	1-5/6	1-5/6	3-2/3	

12. BUDGET ACTIVITY:

RESEARCH

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Marine Biological Laboratory.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NONE.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. N.I.N.D.B. — INSTITUTE
2. Laboratory of Biophysics — LABORATORY OR BRANCH
3. _____ — SECTION
4. _____ — LOCATION
5. NINDB L-46 — SERIAL NO.

6. Correlation of Acetylcholinesterase inhibition spectrum with nerve action.
PROJECT TITLE

7. Moore, J. W.
PRINCIPAL INVESTIGATOR

8. Friess, S. L. (NMRI)
OTHER INVESTIGATORS

9. Project Description:

Objective: To attempt a characterization of the site of action of the drugs. The ultimate objective is to determine the mode of action.

Methods Employed: The depression of the desheathed frog sciatic A fibre propagated action potential on passing through a drug chamber is observed. The ratio of the amplitudes of the impulse before and after passing the drug chamber is observed as a function of time. The velocity change caused by the drug is obtained from the change in the time interval between these impulses.

Major Findings: None.

Significance to NINDB Research: These studies will aid in elucidating the structure of cholinesterase and its role in the function of nerves under normal and disturbed conditions.

Proposed Course: The basic control experiments with AcH have been largely completed along with preliminary findings on the first of the drug series. There are now available a number of these drugs, differing widely in enzymatic activity, but with only small changes in shape and size. It is proposed to continue tests on nerves with these.

R.P.C. - 2
December 1954

Budget Data Sheet

10. NINDB L-46
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	7,300	1/3	1	1-1/3	1/6	1/2	2/3	
FY 1956	8,100	1/3	1	1-1/3	1/3	1	1-1/3	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

Naval Medical Research Institute.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NONE.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. N.I.N.D.B. (INSTITUTE) 2. Laboratory of Biophysics (LABORATORY OR BRANCH)

3. (SECTION) 4. (LOCATION) 5. NINDB L-47 (SERIAL NO.)

6. Ion Permeabilities of Nerve Membranes.
B. Theoretical investigations of the squid giant axon.
PROJECT TITLE

7. Cole, K. S.
PRINCIPAL INVESTIGATOR

8. Antosiewicz, H. A. (NBS); Moore, J. W.
OTHER INVESTIGATORS

9. Project Description:

Objectives: Evaluation of any limits within which the present differential equations may be used to determine the otherwise immeasurable fast ion movements across a normal nerve membrane; empirical modification of the equations for application to abnormal conditions; investigation of the structural and functional bases for the equations.

Methods Employed: Primary reliance will be placed on the National Bureau of Standards digital computer SEAC, which is coded to calculate the electrical potential and ion current responses to a variety of stimuli on the basis of the present equations. Linear and non-linear analogue computers will be employed as available and necessary for analysis and synthesis, using these and other empirical or theoretical equations.

Major Findings: None.

Significance to NINDB Research: The limited comparison between the broad generalizations of electrophysiology and calculations based upon empirical differential equations of normal membrane ion movements have been so satisfactory as to encourage the assumption that these movements and the mechanisms by which they are controlled are a fundamental component of normal and pathological nervous processes.

Proposed Course of Project: SEAC calculations will be made to determine the velocity and wave form of a propagated impulse as a function of temperature and perhaps external sodium concentration. The threshold for simultaneous membrane excitation

will be determined with maximum accuracy to guide a formal analysis of the equations and perhaps as a function of external sodium concentration. An analogue computer under design will be used to calculate the steady state alternating current ionic and membrane admittances and provide a basis for estimating the effect of external ions upon the equation parameters.

The possibility of obtaining faster solutions of the present and other equations under easily varied conditions will be an important factor in the design of a non-linear analogue computer.

R.P.C. - 2
December 1954

Budget Data Sheet

10. NINDB L-47
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	14,300	1½	5/6	2-1/3	3/4	½	1¼	
FY 1956	25,000	1½	5/6	2-1/3	1½	5/6	2-1/3	

12. BUDGET ACTIVITY:

RESEARCH

13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956:

National Bureau of Standards.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NONE.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. N.I.N.D.B. — INSTITUTE
2. Laboratory of Biophysics — LABORATORY OR BRANCH
3. _____ — SECTION
4. _____ — LOCATION
5. NINDB L-48 — SERIAL NO.

6. Laboratory of Biophysics Organization. — PROJECT TITLE

7. Cole, K. S. — PRINCIPAL INVESTIGATOR

8. Moore, J. W. — OTHER INVESTIGATORS

9. Project Description:

Objective: The establishment of an effective laboratory of biophysics to advance the knowledge and support the investigations of neurological diseases and blindness.

Methods: Fundamental and advanced techniques of physics, chemistry and mathematics are used or developed for theoretical and experimental neural problems in their basic, applied and technical aspects.

Major Findings: Planning, development and operation of the laboratory were all in progress by the end of 1954.

Significance to NINDB Research: To the extent that the laboratory can lead, support and follow the biochemical, anatomical, physiological, pathological and clinical approaches, it will constitute an essential facet in the prevention, detection and cure of neurological diseases.

Proposed Course: The initial emphasis is upon the utilization of the available power of the physical sciences in the measurement and interpretation of the rapid ion movements in individual neurones. As necessary and possible, investigations of the physical aspects of aggregate neural structures and theoretical or experimental technical developments may be assisted or initiated.

R.P.C. - 2
December 1954

Budget Data Sheet

10. NINDB L-48
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF.	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	14,800	1/3	1-1/3	1-2/3	1/6	2/3	5/6	
FY 1956	12,000	1/3	1-1/3	1-2/3	1/3	1-1/3	1-2/3	

12. BUDGET ACTIVITY:

RESEARCH

R. P. C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases & Blindness — INSTITUTE
2. Extramural Programs — LABORATORY OR BRANCH
3. _____ — SECTION
4. _____ — LOCATION (IF OTHER THAN BETHESDA)
5. 49 — SERIAL NO.
6. Extramural Programs — PROJECT TITLE
7. Dr. Edward P. Offutt, Chief, Extramural Programs — PRINCIPAL INVESTIGATOR(S)
8. _____ — OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Project: Extramural Programs

Objectives: To increase the quality and quantity of research, teaching, and appreciation of the conditions prevalent in the fields of the neurologic and sensory diseases.

Methods employed: Funds are granted upon application and following competitive review to provide salaries or stipends, equipment, supplies or other necessities to permit research projects or training programs to be conducted.

Major fields of emphasis and results: The Extramural program is considered under its four major divisions, as follows:

1) Research Grant Program: During the calendar year January 1, 1954 through December 31, 1954, 349 research grants-in-aid have been supported through this program. Research projects have been conducted in 112 medical schools and other nonfederal research institutions throughout the country. The total sum involved is $3,540,840. In addition, 66 requests were received which the reviewing committees failed to recommend in competition with more highly regarded projects.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-49
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	53,100	2	6	8	1	5	6	XXX
FY 1956	52,800	2	6	8	2	6	8	XXX

12. BUDGET ACTIVITY:

RESEARCH [ ] ADMINISTRATION [ ]

REVIEW & APPROVAL [X] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH IDICATE SERIAL NO(S)

None providing funds, facilities, or personnel.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE, IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-49
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None originating from this office. Grantees, however, publish freely.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None directly connected with project. Grantees frequently honored.

1) Research Grant Program: (Continued)

The projects supported involve research into the causes, care, and treatment of diseases and conditions of the brain, spinal cord and peripheral nerves, sensory endings, the eye and ear. Such specific diseases as cerebral palsy, muscular dystrophy, epilepsy, and other cerebral vascular accidents, Parkinsonism, glaucoma, cataracts, retrolental fibroplasia and other blinding eye conditions, and hearing impairments are included in projects presently active.

2) Research Fellowship Program: Between January 1, 1954 and December 31, 1954, a total of 40 fellowships awards have been made including 7 predoctoral, 30 postdoctoral, and 3 special fellowships. This program permits holders of fellowship awards to devote full-time to their training as research investigators in the fields of neurologic and sensory diseases and the ancillary disciplines related thereto. The total sum of money involved has been $163,653. In addition, 40 requests have been received which we were not able to activate due to insufficient funds. Also, 3 requests were received which failed to be approved in competition with successful candidates.

3) Training Grants Program: During the period involved, 40 grants totaling $740,512 have been awarded. These are located in 35 medical schools and teaching institutions. There were 5 applications which failed to receive recommendation for approval.

The training grant program is designed to reduce the critical shortage of clinical teachers and clinical investigators by providing funds to teaching institutions to begin or increase their training opportunities in all fields related to neurological and sensory diseases.

4) Traineeship Program: In the period concerned, 43 traineeships have been awarded totaling $145,066, for the purpose of increasing the number of graduate professional personnel available to all branches of medicine and to provide special training in the diagnosis, treatment, and care of neurological and sensory disorders. These 43 men are training in 24 different centers in the United States and England. There were, in addition, 21 approved requests which could not be paid due to lack of funds. These requests totaled $68,800. Unsuccessful candidates numbered 10.

Significance to Neurological research: At present there is an extreme shortage of medical and research manpower available to conduct research and to train new men in the neurologic and sensory disease fields. One of the purposes of the extramural program is to improve this situation.

Proposed course of project: To continue supporting those presently active grants and awards which may be recommended by the scientific and advisory review groups. To institute new grants and awards in order that more medical and research manpower may be trained and encouraged to work in the neurological and sensory disease fields and their allied disciplines of neuroanatomy, neurophysiology, neuropathology, neurobiochemistry, neurology, ophthalmology, otology, and other related fields.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Neurological Diseases & Blindness — INSTITUTE
2. None — BRANCH
3. Publications and Reports — SECTION
4. Not applicable — LOCATION
5. NINDB 50 — SERIAL NO
6. Not applicable — PROJECT TITLE
7. Not applicable — PRINCIPAL INVESTIGATOR (S)
8. Not applicable — OTHER INVESTIGATORS
9. PROJECT DISCRIPTION

It is the responsibility of this section to inform the public or those charged with public care regarding the nature of contemporary knowledge of the neurological and sensory diseases (including research developments), thereby facilitating the improved treatment or prevention of such disorders as epilepsy, multiple sclerosis, cerebral palsy, muscular dystrophy, glaucoma, and cataract.

The section is, therefore, concerned with:
(1) answering public inquiries (approximately 1500 a year on disease entities, research findings, methods and sources of treatment and rehabilitation, and requests for admission to the Clinical Center for participation in research studies);
(2) program reporting to the Department of Health, Education and Welfare and to the Congress (in the form of quarterly and annual reports, research highlights, research progress reports, and prepared testimony for the Congressional appropriations committees);
(3) preparation of special materials for public dissemination (including press releases, exhibits, pamphlets and brochures on neurological and sensory disorders, speeches for presentation by the Institute Director to lay and scientific organizations, and articles on specific disease entities for publication in popular magazines;

(4) apecial projects related to informational activities (including clearance of manuscripts for scientific journals, meetings and other liaison activities with voluntary health organizations, and assistance to science writers interested in articles on the neurological and sensory disorders.

The usefulness of the Publications and Reports Section is obvious: 1) for the patient - guidance to the source of assistance for their problems arising from the neurological and sensory disorders; 2) for the professional man - rapport for learning the latest findings resulting from Institute research, for example, in drug therapy for epilepsy, and retrolental fibroplasia; 3) for the Department of Health, Education, and Welfare and the Congress - clarification of the degree to which the Institute is meeting its responsibilities, and definition of its research activities.

The section foresees the foregoing as the essential elements in its program for the next and future years. During this coming year, we envision completion of several major projects, initiated during the past year. These include a pamphlet on the Institute's activities, a pamphlet on muscular dystrophy to be produced in cooperation with the Muscular Dystrophy Association, and the publication of a monograph on State laws affecting epileptics.

R.P.C. 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB 50
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF.	OTHER	TOTAL	MAN YEARS PROF.	OTHER	TOTAL	PATIENT DAYS
FY 1955	$23,000	1	3	4	1	3	4	
FY 1956	$24,000	1	3	4	1	3	4	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE IDENTIFY SUCH PROJECT.

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheets

15. NINDB 50
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954.

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954.

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases & Blindness (INSTITUTE) 2. Office of Director (LABORATORY OR BRANCH)

3. _____ (SECTION) 4. _____ (LOCATION (IF OTHER THAN BETHESDA) 5. 51 (SERIAL NO.)

6. Administration
PROJECT TITLE

7. Pearce Bailey, M.D., Director and J.H. McLoughlin, Administrative Officer
PRINCIPAL INVESTIGATORS

8. 4 clerks
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This project finances the office of the Institute Director and his immediate staff for the overall program direction and administration for the National Institute of Neurological Diseases and Blindness.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. 51
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	62,000	2	6	8	2	5	7	
FY 1956	62,000	2	6	8	2	6	8	

12. BUDGET ACTIVITY:

ADMINISTRATION

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANI* ZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

Not applicable

R.P.C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Basic Research Program
LABORATORY OR BRANCH

3. --
SECTION

4. ___
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB L-52
SERIAL NO.

6. Fundamental studies on vision and other special senses
PROJECT TITLE

7. ---
PRINCIPAL INVESTIGATOR

8. ---
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The increase in funds over fiscal year 1955 will be used to support studies in the anatomy of the eye and optic tract, the anatomy of the ear, the physiological phenomena associated with vision, audition and the other special senses.

R.P.C. - 2
December 1954 Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB L-52
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS		
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL
FY 1955	--	--	--	--	--	--	--
FY 1956	69,000	3	4	7	--	--	--

12. BUDGET ACTIVITY: RESEARCH

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Basic Research Program
LABORATORY OR BRANCH

3. --
SECTION

4. _____
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-L-53
SERIAL NO.

6. Fundamental studies on the mechanism of neural transmission
PROJECT TITLE

7. ---
PRINCIPAL INVESTIGATOR

8. ---
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

The increase in funds over fiscal year 1955 will be used to support basic biochemical, biophysical and physiological studies on the nerve impulse, its origin, properties, response to drugs, chemical agents, trauma and disease.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB L-53
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS		
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL
FY 1955	--	--	--	--	--	--	--
FY 1956	31,500	2	2	4	--	--	--

12. BUDGET ACTIVITY: RESEARCH

National Institute of Neurological Diseases and Blindness

Clinical Investigations Annual Report

The Clinical Director's Report

The Clinical Investigative Unit of the National Institute of Neurological Diseases and Blindness, in submitting its second annual report, is able to report an activation of 52 beds, all laboratories, and varying degrees of progress on 63 research projects. 314 patients were admitted to the in-patient service and 1,314 to the out-patient service during the period of this report. A full staff is now recruited with the exception of the Branch of Ophthalmology, in which there will be a substantial increase during the coming year. Many and varied neurological and ophthalmological diseases have been studied with some fruitful results. Epilepsy has continued to occupy a large share of the research of this Institute in that the uniqueness of this project and the approach to patients and animals are such that basic information may be correlated with clinical observations. As in the previous year, the medical unit has devoted much of its energy to the disorders of the lower motor neuron. Progress has been made also in studies of demyelinizing disorders, the cerebellar ataxias, amyotrophic lateral sclerosis, and other diseases of the central nervous system. A broad program to further understand the causes and patho-physiology of cerebral palsy has been initiated. Infections of acute and chronic nature of the eye and studies of cataract, glaucoma, and strabismus have continued. More specifically the following research is of note.

In the field of muscular dystrophy, it has been demonstrated by Doctors Berg, Horvath and Shy that there is a leakage of potassium from the residual muscle fibers and a retention of sodium. It has been demonstrated by radioactive isotopic technique that such ionic imbalance is not, however, the etiological agent in muscular dystrophy but a result of the disease. It has been suggested by the same authors that there is an abnormal release of protein bound iodine from the blood vessels of the dystrophic patient. It has not been determined, however, whether this release is due to intra or extra vascular fragmentation of the protein at this time. The loss of such potassium may be expected to make such muscle fibers hyperirritable and to contract spontaneously, and Doctors Chatfield and Norris have demonstrated that indeed this is so. The spontaneous irritability in muscular dystrophy patients after contraction explains much in the correlation of those dystrophies with myotonia and those without, and it would appear indeed that myotonia is present in each. The presence of spontaneous action potential of short duration and small amplitude throws a serious question as to the utilization of the electromyogram to differentiate diseases of nerve from diseases of muscle. Doctor Tower and Mr. Pogorelskin for the first time have quantitated the pentose excretion in muscular dystrophy and demonstrated this to be ribose by paper chromotography. Confusion still exists between the so-called nutritional dystrophies in animals, and myositis and muscular dystrophy in man. Examination of some 80 odd biopsies by numerous staining techniques throws considerable question

as to whether indeed the two processes are different. The distinguished neuropathologist, Doctor J. Godwin Greenfield of England, has joined Doctors Alvord, Berg, and Shy in a study in this regard. Doctor Horvath is continuing his basic work in extraction of actin and myosin from all patients with neuromuscular diseases, including muscular dystrophy, in the determination of tensile strengths of isolated muscle fibers and in the study of myotonia in both man and goat. He is developing new methods for the extraction of actin and checking these against micro-nitrogen determinations. Myasthenia gravis has continued to occupy much of the research team's time and recent experiments in animals by Doctors Irwin, Berg, and Shy lead to the suggestion of a possibility of a circulating depolarizing agent in this disease. If this basic experimentation is applicable to man, then prostigmine would no longer be the drug of choice in this disease. It is anticipated the transference of this work to human subjects will be accomplished within the next few months. Such theories are also compatible with the findings of Doctors Rowland, Berg, Korengold, and Shy as to the increased weakness occurring in myasthenics receiving prostigmine. Seven manuscripts have been released over the past year in the field of neuromuscular research. Doctor Korengold and Doctor Norris have continued their work on electromyography in myasthenia and in muscle cramps. Doctors Norris and Chatfield have demonstrated that muscle cramps originate largely from the spinal cord and, concerning this observation, there is a paper now in press.

The demonstration that patients with cerebellar atazia may carry an abnormal globulin in their circulating serum has lead the unit to investigate by paper electrophoresis the protein chemistry of patients with this disease. Similar studies are being carried out in patients with demyelinizing diseases in both serum and spinal fluid by Doctors Jaffee and Tower. The report of a limited number of cases with multiple sclerosis responding to iso-nicotinic acid hydrazide from a Veterans' Administration Hospital has lead to a controlled study in this Institute of 30 unequivocal multiple sclerosis patients who have received this substance. To date, unfortunately, initial claims have not been substantiated by this Unit. This study is being carried out by Doctors Haase, Korengold, and Berg. The observation that spinal fluid sugar may be lowered in virus disorders of the central nervous system has lead Doctor Berg to further studies of the utilization of glucose in these diseases. In this regard, the glucose is tagged with carbon 14. Doctor Korengold is continuing his work on ganglionic blocking agents in paraplegia and other neurological disorders associated with spasm.

During the past year the Branch of Surgical Neurology has continued its investigation of the temporal lobe and its environs in man, in higher primates, and cats. In man such investigations were concerned with epileptic processes in the temporal lobe, the surgical

treatment of these processes, and to the development to the further understanding of the function of the temporal lobe. An intensive study of psychological aspects and the psychological problems of patients with temporal lobe lesions has been continued. The temporal lobe itself is concerned with fundamental mechanisms of mind, such as perception, judgement, and memory. Again, this has been a group investigation of varied disciplines with a goal toward a single purpose. The team consists of medical and surgical neurologists, clinical psychologists, clinical neurophysiologists, neuropathologists, and neurochemists. Many patients, after thorough investigations, have undergone radical treatment for their seizures. The essential epileptogenic lesion was localized by electrographic recording and direct electrical stimulation. The results of these recordings and stimulations are useful not only for the purpose of diagnosis, but to further the physiological understanding of the temporal lobe as well. As these investigations have progressed, Doctor Baldwin and his team have become more and more involved in subcortical seizure patterns originating from the amygdaloid nucleus and hippocampus as well as the temporal pole. This nucleus appears to be an essential relay station within the temporal lobe and has functions in man and primates with the movement of face and jaws, as well as control of respiration and blood pressure. It is intimately concerned with the mechanism of consciousness as well. Temporal lobe seizures in monkeys and chimpanzees, and their study in conditioned primates, have been continued by Doctors Baldwin, Frost, Ralston, Van Buren, and Wood. Patients who have undergone subtotal temporal lobectomy have been studied at length in this regard as well as in speech. Doctors Lord and Baldwin have suggestive evidence for the first time of localization in a discriminatory pattern of auditory stimuli to the dominant hemisphere in man. The complicated and diverse information on the psychological functions of the temporal lobe will be reported at the Neurosurgical Session of the American College of Surgeons in Lima, Peru on January 15th. To adequately understand epilepsy itself, regardless of its site, one must know the basic physiology and chemistry of the involved cell. Doctor Tower and his colleagues have continued their work on the in vitro brain slices taken from Doctor Baldwin's cases. Doctor Tower and Doctor Wells have, in combination with six large extramural centers, launched a program as to the effectiveness of glutamine and asparagine and the reversal of seizures in man. Doctor Tower's work in this regard has been published during the past year and presented to the American Academy of Neurology. Doctor Curtis, working with Doctor Tower, has developed a method of determining glutamine, asparagine, glutamic acid, and aspartic acid on the same specimen. The initial results that Doctor Tower presents are promising, as are those from two of the contributing centers. To further understand the electroencephalographic evidence of seizures, we have had join us the distinguished visiting scientist, Doctor Choh Luh Li, who is carrying on recordings from single cortical cells by means of potassium chloride micro-electrodes. Doctor Li has developed an apparatus to allow the electrode to remain in situ in spite of brain pulsations for as long as 5 minutes within a single cell.

Doctor Ajmone Marsan and Doctor Tower are carrying on electroencephalographic studies in patients receiving these essential amino acids. Doctor Chatfield has demonstrated within the past year that atropine activation of the cerebral cortex is not due presumably to the release of acetylcholine, but is probably due to a blockade by atropine of inhibitory centers lying deep within the brain. Doctor Ajmone Marsan has carried on his fundamental research of the inter action of the nonspecific and specific thalamic nuclei and their relation to the recruitment response. This latter study may be of significant value in determining the ability of subjects to concentrate to a given type of sensation such as sound, although other sensations are about him such as sight and touch. Doctor Ajmone Marsan and Doctor Baldwin are also extensively studying the electrocortigram of patients with seizures and it is hoped in the coming year that micro-electrode recording from human "epileptic" cortex will be achieved with the addition of Doctor Li to this scientific team. Mr. Woods has demonstrated a marked effect on respiration in the claustrum. This nucleus had no known function to date. The effect of transmission of epileptic discharge from one temporal lobe to the opposite has been a difficult clinical problem. Studies in this regard in higher primates have been carried out by Doctor Baldwin and his team in sectioning of the anterior commissure. Doctor Van Buren is doing work on visual system in retrograde lesions in man.

The section of Neuropathology has aided in all the studies and Doctor Alvord and Doctor Greenfield are studying the cytological changes of the removed epileptic cortex. Doctor Alvord has also worked with Doctor Goldstein from the Institute of Mental Health in the chemistry and pathology of induced "allergic" encephalomyelitis. Doctor Alvord and Doctor Brace of the National Cancer Institute are carrying on extensive experiments of high dosages of radiation to the nervous system and a similar study between Doctor Alvord and Doctor Lilly of the National Institute of Mental Health in electric shock therapy is underway. Doctor Alvord and Doctor Whitlock of the Army Medical Center have continued their fundamental work in the startle reaction and this work is also now almost ready for publication.

Doctor Irwin and Mr. Wells have succeeded in establishing cross circulation experiments between dogs after much initial difficulty due to the distribution of the anterior spinal artery to the medulla oblongata. Their results also are near publication and demonstrate that these ganglionic blocking agents probably do not have a central action as has been reported previously. They have also demonstrated that calcium metabolism is important in neuromuscular blocking agents and that such blocks may be successfully broken by the administration of calcium or perpetuated by the infusion of the chelating substance, ethylene diamine tetra-acetic acid.

The Ophthalmological Branch, in spite of its limitations, has had a fruitful year. In combination with the team from the National Institute of Microbiology they have done extensive studies in posterior granulomatous uveitis and its relation to toxoplasmosis. A report on the apparent successful therapy in a series of such cases was given at the American Academy of Ophthalmology. The Branch is now entering its second phase

of this study in determining body fluid and tissue levels of pyrimethamine. A new disease entity now called Adenoidal-Pharyngeal-Conjunctival virus was established during the year. The ophthalmological characteristics of this disease was reported in the Sight Saving Review in December, 1954. Other studies underway in this Branch are the clinical phases of cataract research, glaucoma, strabismus, and the value of l-asparagine in the treatment of retinitis pigmentosa. Projects have been organized in electroretinography and ocular tumors. Studies of penetration of cortisone in the eye have been carried out, utilizing carbon 14. Such studies indicate that such cortisone does not reach the posterior chamber. An instrument improvement project has been carried on by Doctors Gunkel and Ryan with a greatly improved self recording tangent screen being developed. Doctor Resnik has continued his basic research in the sulfa hydrial metabolism of cataracts in alloxan diabetes.

The finding by Doctor Kurland of an incidence of amyotrophic lateral sclerosis that is at least 100 times as prevalent as other population groups on the Island of Guam has lead to a major project of combined studies encompassing the Public Health Service, the Navy, the Government of Guam, and the Mayo Clinic, under the direction of Doctor Kurland. This has been a fruitful study to date with some 5 reports being published. The studies include, other than the epidemiology, a clinical and therapeutic study, a pathological anatomy study by Doctor Sayre of the Mayo Clinic, a clinical pathological study by Doctor Gerundo of the Guam Government, electromyographic studies by Doctor Lambert of the Mayo Clinic, gastric cytology studies by Doctor Rubin of Washington State University, and nutritional studies by Doctor Whiting of the Harvard School of Public Health. It would appear in the original studies that the most likely factor here is genetic but additional studies as to nutritional background and as to why it is prevalent among the Chamorros population are being conducted. There is a suggestion that it may have been introduced to the Island around 1700, at the time of the conquest of the Island by Spain. This is the first indication on a large scale that amyotrophic lateral sclerosis may carry a hereditary element. Doctor Kurland and his colleagues have published 5 papers in the past year on this disease in several journals.

Doctor Kurland and Doctor Berkson of the Division of Biometry of the Mayo Clinic are continuing their studies of epidemiological surveys of chronic neurological diseases in the United States and Canada. A "pilot" study has been completed at Rochester, Minnesota, and it is anticipated that the next study is in a city of the same size in Canada. The initial report has been published by Doctor Kurland in the Annals of the New York Academy of Sciences.

Cerebral Palsy will be studied on a much larger scale in the coming years. In the past year such studies have been limited in the

Branch of Surgical Neurology by a combined study of Doctors Baldwin, Alvord, and Ajmone Marsan on the clinical, electroencephalographic, and pathological characteristics of massive hemispherical lesions. Such patients have undergone hemispherectomies. In the coming year this program will be expanded to include a cooperative venture with a number of other hospitals and institutions through the research grant program under the direction of Doctor Bailey and coordination of Doctor Imus. Doctor Anatole Dekaban will join the Institute in the near future in charge of the research in the Bethesda area. Doctor Dekaban will be interested in the embryological malformations and is an expert in this field as well as in clinical neurology. Doctor Greenfield and Doctor Alvord will continue with the neuropathological studies, and fundamental research in animals will be carried on by Doctors Windle and Dekaban.

Twenty-seven manuscripts are in preparation or have been submitted and published during the past year from the Clinical Investigative Unit of this Institute, covering the wide range of diseases described above. It is anticipated that the next year will be even more productive.

G. Milton Shy, M. D.

R.P.C. 1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Medical Neurology — BRANCH
3. Neurological Disorders Service — SECTION
4. - — LOCATION
5. NINDB-1 (C) — SERIAL NO.

6. Studies in the Pharmacology of Myasthenia Gravis and Studies in Prostigmine Tolerance — PROJECT TITLE

7. G. Milton Shy, M. D. — PRINCIPAL INVESTIGATOR

8. L. P. Rowland, M. D., ~~Donald B. Tower, M. D.~~ Richard L. Brown, Ph.D, Leonard Berg, M.D. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: In the treatment of myasthenia gravis, one item of essential information has long been lacking, and to a certain extent, a matter of controversy. It is known that in many myasthenics assistance cannot be afforded by large amounts of prostigmine, and, in others, symptoms may become so severe that the patient dies despite the administration of large amounts of this drug, which is presumably almost specific treatment for the disease. It has been the opinion of some investigators that this occurs merely because the patients are receiving an insufficient amount of prostigmine. Others have held the opinion that the patients are actually refractory to the drug; and some have feared to give large amounts of the drug because of possible adverse affects on muscle strength; ie, the patient might become weaker rather than stronger. Because critical data on this problem are lacking, the following investigation is contemplated and underway.

Method employed: To myasthenic patients with varying degrees of severity of the disease, injections of prostigmine are given over a period of several hours. At first, only small amounts are used and this is gradually increased. This is continued until the patient achieves an optimal response in terms of increased strength. Concomitantly the likelihood for annoying side effects are observed. At this point, the injection is gradually increased to see how long the optimal state can be maintained and what happens beyond this point. Correlated with this study are measurements of serum cholinesterase and evaluation of the response of muscle to nerve stimulation.

NINDB-1 (C)
SERIAL NO.

Patient Material:

		No.	Avg. Stay Days
Admissions:	Adult males	6	24.2
	Adult females	4	53.1
	Children male	0	-
	Children females	0	-
Outpatients:	Number of patients	0	
	Number of visits	-	

Major findings: Recently this group of investigators have attempted to correlate all known information on myasthenia gravis into a plausible scheme and to attempt animal experimentation and subsequent human experimentation to demonstrate the plausibility of this scheme. If one searches for a depolarizing type of agent such as decamethonium in the myasthenic patient instead of nondepolarizing agent such as curare, then all research work in myasthenia gravis can be fitted into one scheme. Repetitive dosages of decamethonium will change the block from a depolarizing type of block to a competitive block. Some muscles are more sensitive to this than are others and these are primarily the muscles affected in myasthenia gravis. In muscles not so affected, however, an increased tolerance to decamethonium occurs as has been demonstrated by Churchill-Davidson in England, whereas those muscles affected to the point that a competitive block exists will become worse. It would be at this stage that myasthenia gravis would present. At this stage prostigmine will reverse the competitive block and we have done such in the laboratory. If one increases the competitive block to the point that only 5% of the twitch potential remains, then prostigmine or tensilon will not reverse this block. However, results in this laboratory demonstrate that hexamethonium will. At the point at which a depolarizing blockade becomes a competitive blockade, tetanus will no longer be held and will increase the blockade as shown in this laboratory. Curare itself acts as a competitive blockade. Further studies, then, must show if hexamethonium will act against curare as well as against decamethonium. If so, this will be the drug of choice in myasthenia gravis. This would also explain why the muscle of a myasthenic not affected by the disease is not resistant to decamethonium while those affected are not susceptible. It will also explain why some myasthenics react at some stages to prostigmine and not to others. Extracts of the thymus also give a blockade which resembles the depolarizing blockage and not a curarizing blockade. Thus, if this work is substantiated within the next few months, the etiology of myasthenia and its treatment will be considerable clarified. At this point, however, no conclusions should be drawn until further experimental work has been done.

Significance to neurological research: Primary studies on a few patients indicated that in some patients, at least, adverse symptoms will appear before myasthenia symptoms can be completely relieved, even when an attempt is made to control these side effects by the

administration of specific antidotes. Among the adverse symptoms which have been noted is the decline in muscle strength, even greater than the weakness prior to the administration of prostigmine. If further study can corroborate these findings or further analyze them, that should have significant implications for the treatment of the disease and may cast some light on the nature of the disease.

Proposed course of the project: Related to this and contemplated for the future is the evaluation of different drugs none to affect the neuromuscular junction when given by the intra-arterial route.

R.P.C. 2
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-1 (C)
SERIAL NO.

11. BUDGET DATA

	EST. EXPEND.	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	$6,500	3	--	3	0.7	--	0.7	
FY 1956	$7,500	3	--	3	0.7	--	0.7	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.

-

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE IDENTIFY SUCH PROJECT.

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R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-1 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Rowland, L. P. et al: Prostigmine Induced Muscle Weakness in Patients with Myasthenia Gravis: Preliminary Report. J. of Neurology (to be published).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

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R.P.C. 1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness (INSTITUTE) 2. Medical Neurology (BRANCH)

3. Neurological Disorders Service (SECTION) 4. - (LOCATION) 5. NINDB-2 (C) (SERIAL NO.)

6. Correlation of Electromyography, Clinical Diagnosis, and Pathology of Muscle Disease (PROJECT TITLE)

7. G. Milton Shy, M. D. (PRINCIPAL INVESTIGATOR)

8. Paul O. Chatfield, M. D., Marvin C. Korengold, M. D., Ted Norris (OTHER INVESTIGATORS)

9. PROJECT DESCRIPTION

Objective: To place electromyography on a firm physio-pathological basis in relation to neuromuscular disease.

Method employed: Tentative clinical impressions will be recorded as to wasting of muscle being a dystrophic or neurotrophic process. The involved musculature will be scaled by polio foundation classification. Electromyographic recordings will be obtained from that muscle most affected by clinical evaluation. This site will be marked and a biopsy obtained under local anesthesia. The biopsy will be assessed in respect to the clinical diagnosis, the electromyographic impressions, and evaluation of all such procedures determined. This program was initiated at the National Hospital, Queen Square, London, where the first 31 cases were recorded in conjunction with Doctor Blackwood, Pathologist to the National Hospital. We are now recording from two 100 square micra monopolar electrodes.

Patient material:

		No.	Avg. Stay Days
Admissions:	Adult males	45	39.6
	Adult females	42	43.5
	Children male	19	32.2
	Children female	3	19.0
Outpatient:	Number of patients	0	
	Number of visits	-	

Major findings: It has been demonstrated to the satisfaction of the investigators that short duration potentials accruing from isolated muscle fibers do not of necessity result purely from

the denervation but may, in fact, arise from any number of myopathies which may similarly make the muscle more sensitive to external stimulii. Thus, myotonic-like pictures have been obtained from all types of muscular dystrophies. This tends to resolve one of the paramount questions of neurology as to why some dystrophies should have myotonia and some should not.

Significance to Neurological research: See objective.

Proposed Course of Project: Continuation of this project is anticipated as well as the preparation of a paper for publication of results.

R.P.C. 2
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-2 (C)
SERIAL NO.

11. BUDGET DATA

	EST. EXPEND.	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	$6,500	3	--	3	0.7	--	0.7	
FY 1956	$7,500	3	--	3	0.7	--	0.7	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.

-

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE IDENTIFY SUCH PROJECT.

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R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-2 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

-

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

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Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness (INSTITUTE) 2. Medical Neurology (BRANCH)

3. Neurological Disorders Service (SECTION) 4. - (LOCATION) 5. NINDB-3 (C) (SERIAL NO.)

6. Ionic Exchange in Neuromuscular Disease
PROJECT TITLE

7. G. Milton Shy, M. D.
PRINCIPAL INVESTIGATOR

8. Beni Horvath, M.D., Leonard Berg, M. D., Donald Cummings
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objective: Proposed plan to determine the effect of potassium metabolism, in particular, intracellular concentrations of potassium in neuromuscular disorders, by the use of tracer elements and flame photometry and the utilization of specific pharmacological agents.

Method employed: Clinical material will be subjects with muscular dystrophy, myasthenia gravis, myotonia, and myositis. Biopsies will be removed from such subjects under major nerve block. Our modification of the Boyle-Conway technique will be used for extracellular space. This procedure will continue to be controlled by conscientious objectors. Animal experimentation will be continued in rabbits, rats and guinea pigs, the experimentation on goats having now been terminated.

Patient material:

		No.	Avg. Stay Days
Admissions:	Adult males	18	36.2
	Adult females	25	34.8
	Children male	14	33.6
	Children Female	1	15.0
Outpatient:	Number of patients	0	
	Number of visits	-	

Major findings: Within the last year this unit has established a technique whereby the sodium and potassium of residual muscle and the amount of potassium exchanged in residual muscle can be determined in various diseases. In muscular dystrophy it has been demonstrated that potassium is low and sodium is high, and a regression curve may be drawn between the two. In spite of this, however, the potassium turnover of microcuries per milliequivalent is within the range of normal demonstrating this result to be the effect and not the cause of the disease. In

9. PROJECT DESCRIPTION (Continued)

myasthenia gravis this technique has been utilized to demonstrate that the defect in potassium lies in an inability to enter the cell or an excess leakage from the cell. The first has been related to the anticholine esterase groupe of drugs and the second to the choline acetylase system. Initial results of this were reported at the Myasthenia Gravis Foundation Conference.

Significance to Neurological Research: It is anticipated that the role of potassium exchange is much more important to the general problem of myasthenia, myotonia and muscle wasting than the individual analysis of the potassium level of serum or urine at any one time. The relationship extends to the field of endocrine and metabolic disorders as well as specific neuromuscular disorders.

Proposed course of project: Continuation of this project and publication of papers demonstrating the results of this project.

R.P.C. 2
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-3 (C)
SERIAL NO.

11. BUDGET DATA

	EST. EXPEND.	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	$10,200	2	1	3	0.2	0.5	0.7	
FY 1956	$11,800	2	1	3	0.7	0.3	1.0	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.

-

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE IDENTIFY SUCH PROJECT.

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R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-3 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

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Project Description Sheet

1. Neurology — INSTITUTE
2. Medical Neurology — LABORATORY OR BRANCH
3. Neurological Disorders Service — SECTION
4. _____ — LOCATION
5. NINDB-4(C) — SERIAL NO.

6. An Investigation of the Relationship Between Blood and Spinal Fluid Glucose.
PROJECT TITLE

7. Leonard Berg, M. D.
PRINCIPAL INVESTIGATOR

8. G. M. Shy, M. D. and Donald Cummings
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Project: An investigation of the relationship between blood and spinal fluid glucose.

Objectives: 1. Elucidation of mechanisms of glucose transfer across blood-fluid barriers, of glucose utilization in brain and spinal fluid in normal and disease states.
2. Elucidation of details of cerebrospinal fluid function.

Methods Employed: The quantity of glucose and its degradation products in the spinal fluid will be followed during experimentally produced changes in the blood glucose. Experiments will be performed on suitable laboratory animals in their normal state as well as during various kinds of meningitis. A new experimental method, namely the use of radioactive glucose to follow glucose metabolism of spinal fluid, will be introduced after preliminary utilizing non-radioactive techniques.

Major Findings: Methods have been developed for the identification, elimination and isolation of glucose in plasma and spinal fluid. Isolation of the compound was necessary primary to the tracing of radioactive glucose because of the obvious necessity of separating the parent compound from radioactive degradation products for counting purposes. Thus far the work has been confined to in vitro experiments. The methods and yields appear to be satisfactory.

Significance to NEUROLOGY Research: It is expected that information will be gained relative to general problems of cerebrospinal fluid physiology. Advances in knowledge about mechanisms and treatment of meningitis and hydrocephalus are goals of this project.

Proposed Course of Project: It is expected that in vivo experiments will shortly be undertaken with the objectives listed above.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-4(C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$8,800	2	1	3	0.6	0.5	1.1	
FY 1956	$10,150	2	1	3	0.7	0.3	1.0	

12. BUDGET ACTIVITY:

RESEARCH [x] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S).

NONE.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-4 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

NONE.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurology — INSTITUTE
2. Medical Neurology — LABORATORY OR BRANCH
3. Neurological Disorders Service — SECTION
4. _____ — LOCATION
5. NINDB-5 (C) — SERIAL NO.

6. Experimental Reduction of Reflex Activity in Special Disease States
PROJECT TITLE

7. M. C. Korengold, M. D.
PRINCIPAL INVESTIGATOR

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Project: Experimental Reduction of Reflex Activity in Special Disease States.

Objectives: To determine response of reflex activity in specially prepared laboratory animals to various drugs in an attempt to achieve a reduction in this activity.

Methods Employed: With the use of suitable laboratory animals, experimental transection procedures are performed. Correlations are to be made between state of their reflex activity as influenced by various neuromuscular blocking agents. Of particular interest will be response to various curare and synthetic curare-like preparations, such as d-tubocurarine, repository tubocurarine, flakedil, succinyl choline, metubine, and syncurine. A study will be made of effects of such medication upon the reflex activity, as well as any associated side reactions involving other areas of the animal.

Major Findings: None.

Significance to NEUROLOGICAL Research: It would be of considerable value to learn more about the use of blocking agents in diseases in which spasticity is a major disability. This would be of value in elucidating further information about the nature of tone and factors that might influence it.

Proposed Course of Project: No change.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-5 (C)
SERIAL NO.

11. BUDGET DATA:

	EST. EXPEND.	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$8,500	1	--	1	1.0	--	1.0	
FY 1956	$9,800	1	--	1	1.0	--	1.0	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S).

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-5 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurology — INSTITUTE
2. Medical Neurology — LABORATORY OR BRANCH
3. Neurological Disorders Service — SECTION
4. _____ — LOCATION
5. NINDB-6 (C) — SERIAL NO.

6. Protein Studies in the Hereditary Ataxias. — PROJECT TITLE

7. M. C. Korengold, M. D. — PRINCIPAL INVESTIGATOR

8. I. Jaffe, M. D. and C. Wells, M. D. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Project: Protein studies in the hereditary ataxias.

Objectives: To determine the qualitative and quantitative protein components of the cerebral spinal fluid and their relationship to serum proteins and other examinations of protein normalcy.

Methods Employed: Patients are to be suitably screened in the Out-Patient Department for disease consistent with the diagnosis of Cerebellar Ataxia. These people will then be admitted as in-patients and blood studies consisting of total and fractional proteins, cephalin flocculation, and thymol turbidities will be run. Spinal fluid will be examined for its differential protein content by means of paper electrophoresis. Similar studies will be run on serum by means of paper electrophoresis, so that adequate comparisons can be made on the significance of protein abnormalities appearing in either area.

Patient Material: (1954 calendar year)

		No.	Average Stay Days
Admissions:	Adult males	2	14.5
	Adult females	3	15
	Children male	1	5
	Children female	-	-
Outpatient:	Number of patients	2	
	Number of visits	2	

Major Findings: As yet not determined.

Significance to NEUROLOGICAL Research: To assist in learning new information about a system disease that may prove of value in correlating protein abnormalities in this condition with chemical abnormalities found in other demyelinizing states. This may lead to previously undescribed abnormalities that may be of value in better understanding the nature of this disease and assist in providing a clue for possible future therapy.

Proposed Course of Project: An increasingly larger number of patients will be admitted to this study and further attempts will be made to correlate differences between those of hereditary nature as opposed to those of a sporadic nature.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-6 (C)
SERIAL NO.

11. BUDGET DATA:

	EST. EXPEND.	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$6,500	3	--	3	0.8	--	0.8	
FY 1956	$7,500	3	--	3	1.2	--	1.2	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S).

NHI - Dr. Jaffe

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publication Sheet

15. NINDB-6 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C. 1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness (INSTITUTE) 2. Surgical Neurology (BRANCH)

3. Clinical Neuropathology (SECTION) 4. _____ (LOCATION) 5. NINDB-7 (C) (SERIAL NO.)

6. Histopathologic investigation of muscular dystrophy and other neuromuscular diseases
PROJECT TITLE

7. Ellsworth C. Alvord, Jr., M. D., G. Milton Shy, M. D., and J. G. Greenfield, M.D.
PRINCIPAL INVESTIGATORS

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To determine the histopathologic correlates of various clinical disorders of the neuromuscular system.

Methods Employed: Sections of muscle and peripheral nerve are examined following paraffin embedding or frozen sectioning with a variety of techniques to demonstrate cross striations, nuclei, connective tissue, endomesial reticulin, nerve axons and lipids.

Patient Material: Patients are obtained from the Medical Neurology Branch, NINDB.

Major Findings: 80 muscle biopsies from a variety of neuromuscular disorders, including muscular dystrophy, myasthenia gravis, and various types of peripheral neuropathy, have been received and are being studied to determine specific abnormalities in these conditions. In a few patients repeated biopsies have been performed in an attempt to determine the regenerative capacity of diseased muscle fibers. Unfortunately, many of these cases have not been completed because of the shortage of adequately trained histopathologic technicians.

Significance to Neurological Research: The determination of the precise morphologic abnormality in peripheral nerves and muscles of patients with clinical disorders of these structures is of great importance in the diagnosis and management of such patients. By the careful correlation of precise clinical and pathologic observations, it should be possible to arrive at a more satisfactory classification of such disorders as well as the planning of further research into the cause and pathogenesis of such diseases.

Proposed Course of Project: With the acquisition of sufficiently well trained personnel all of these cases will be critically studied with the techniques mentioned above and with the development of newer techniques for the demonstration of motor end-plates.

R.P.C. 2
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-7 (C)
SERIAL NO.

11. BUDGET DATA

	EST. EXPEND.	BUDGETED POSITIONS PROF.	OTHER	TOTAL	MAN YEARS PROF.	OTHER	TOTAL	PATIENT DAYS
FY 1955	$7,630	3	3	6	0.3	1.1	1.4	
FY 1956	$7750	3	3	6	0.3	1.1	1.4	

12. BUDGET ACTIVITY:

RESEARCH [x] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.

Medical Neurology Branch, Drs. Shy and Greenfield.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE IDENTIFY SUCH PROJECT.

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-7 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurology (INSTITUTE) 2. Medical Neurology (LABORATORY OR BRANCH)

3. Neurological Disorders Service (SECTION) 4. _____ (LOCATION) 5. NINDB-8 (C) (SERIAL NO.)

6. Study of the short-term effect of INH on the course of Multiple Sclerosis.
PROJECT TITLE

7. G. R. Haase, M. D. and M. C. Korengold, M. D.
PRINCIPAL INVESTIGATORS

8. Kenneth R. Magee, M. D. and Leonard Berg, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Project: Study of the short-term effect of INH on the course of Multiple Sclerosis, which were described as dramatic in a recent study. (The Effects of Isoniazed on Patients with Multiple Sclerosis, Kurtzke and Berlin, The Am. Rev. of Tuberculosis, Vol. 70, No. 4, October, 1954.)

Methods employed: This is a clinical study. Patients who are clearly afflicted with Multiple Sclerosis are being followed as in- and outpatients. The total patient group is divided into two sub-groups, which are matched as nearly as possible. Employing the "double-blind method", one sub-group receives INH while the control group receives a placebo. Both groups are re-examined frequently to determine any alterations in the patient's status. The criteria for inclusion in the study include a clear-cut dissemination of lesions within the central nervous system and a dissemination in the onset of various unrelated symptoms in time. Such patients in whom the diagnosis is questionable have been excluded from participation in the study.

Patient Material: (1954 calendar year)

		No.	Average Stay Days
Admissions:	Adult males	6	82.2
	Adult females	5	52.4
	Children male	-	-
	Children female	-	-
Outpatient:	Number of patients	18	
	Number of visits	107	

Major Findings: To date no clear-cut effect of the medication on the participating patients has been noted.

Significance to NEUROLOGICAL Research: As yet not determined.

Proposed course of project: The study is to be continued until a total of 30 patients with Multiple Sclerosis have received the drug or the control placebo. The study will then only be continued if significant beneficial effects on Multiple Sclerosis have been demonstrated.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-8 (C)
SERIAL NO.

11. BUDGET DATA:

	EST. EXPEND.	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT
FY 1955	$10,900	4	1	5	1.0	--	1.0	
FY 1956	$12,500	4	1	5	1.0	0.4	1.4	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S).

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-8 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Medical Neurology — LOCATION OR BRANCH

3. Clinical Neurophysiology — SECTION
4. _____ — LOCATION (IF OTHER)
5. NINDB-9 (C) — SERIAL NO.

6. Effect of temperature on neuromuscular transmission — PROJECT TITLE

7. Paul O. Chatfield, M.D. — PRINCIPAL INVESTIGATOR

8. None — OTHER INVESTIGATOR(S)

9. PROJECT DESCRIPTION

OBJECTIVES:

It seems desirable to study the effects of temperature on neuromuscular transmission, both from the standpoint of general physiological interest and because some clinical states of neuromuscular disorder are adversely affected when the patient is exposed to the cold.

METHODS EMPLOYED:

The anesthetized experimental animal (rat, hamster) or unanesthetized hibernating hamster is placed in a refrigerated box within which the temperature can be lowered a chosen amount (about 2 degrees centigrade in these experiments). The temperature of this box is thermostatically controlled so that it remains relatively constant. A sciatic nerve is exposed, placed upon stimulating electrodes and ligated, and crushed proximal to the electrodes. The gastrocnemius muscle of the same leg is freed from its insertion at the ankle and its tendon attached to a strain gauge for isometric recording of muscular contraction. The potential changes from the strain gauge are led into a DC amplifier and then recorded photographically with a cathode ray oscilloscope. Two fine wire electrodes are also inserted into the muscle and after suitable amplification the gross muscle action potential is recorded on the second beam of the oscilloscope. The temperature of the muscle is measured with

METHODS EMPLOYED, Cont'd.

a thermocouple leading into a bridge circuit and recording galvanometer. In this way the mechanical and electrical events occurring in the muscle as the result of stimulation of the sciatic nerve can be studied as a function of the temperature of the muscle.

MAJOR FINDINGS

During the past year only pilot experiments have been done in this project, using the rat as a test animal. Preliminary results have confirmed information already available, to wit that a lower frequency of stimulation is necessary to obtain a complete tetanus in a cool muscle than in one at normal body temperature.

SIGNIFICANCE OF THE PROGRAM TO THE INSTITUTE

Since one of the major interests of this institute is the large and varied group of diseases of the neuromuscular system and since some of these disorders are affected by cold, it seems of interest to try to define more clearly the exact effects which temperature has on neuromuscular function.

PROPOSED COURSE OF PROJECT

It is planned to amplify the experiments which have already been performed on the rat and to continue these studies on hamsters arousing from hibernation, i.e. those automatically changing their body temperature from low to high values as well as in anesthetized non-hibernating hamsters whose body temperature can be altered over a wide range without the procedure being lethal to the animal.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-9 (C)
SERIAL NO.

11. BUDGET DATA.

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$4,400	1	1	2	0.2	0.7	0.9	
FY 1956	$5,775	1	1	2	0.2	0.7	0.9	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. IF WITHIN NIH)

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-9 (C)
SERIAL NO.

None

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Medical Neurology — LOCATION OR BRANCH

3. Clinical Neurophysiology — SECTION
4. _____ — Location
5. NINDB-10(C) — SERIAL NO.

6. Effects of topically applied atropine, prostigmine and acetylcholine on evoked cortical potentials
PROJECT TITLE

7. Paul O. Chatfield, M.D.
PRINCIPAL INVESTIGATOR

8. John T. Lord, M.D.
OTHER INVESTIGATOR(S)

9. PROJECT DESCRIPTION

OBJECTIVES

The principal investigator had previously shown in collaboration with Dr. Dominick P. Purpura, now at The Presbyterian Hospital in New York City, that atropine, prostigmine and acetylcholine topically applied to the cerebral cortex of the anesthetized cat markedly augmented evoked cortical potentials whereas prostigmine and acetylcholine applied without prior atropinization of the cortex often depressed these potentials. It was also shown that atropine alone had a potentiating action. The question was raised by Dr. Wade H. Marshall that this being so the reported results might be attributable to the action of atropine by itself with prostigmine and acetylcholine playing no role. Hence this project concerned itself with a resolution of this question.

METHODS EMPLOYED

Cats were used, anesthetized with nembutal. After the insertion of a tracheal cannular a radial nerve was exposed in the upper leg, placed upon stimulating electrodes and ligated and crushed distally to the electrodes. The contralateral foreleg, sensory cortex I was then exposed. Recording from this area was by the monopolar method using a silver wire electrode mounted in a micro manipulator so that it could be raised from the cortex, and then returned to exactly the same spot. Cortical potentials

9. PROJECT DESCRIPTION, Cont'd.

METHODS EMPLOYED

were amplified in the usual way and recorded photographically on a cathode ray oscilloscope. 2% solutions of atropine, prostigmine and acetylcholine were applied to the area of cortex giving the largest positive effect response to stimulation of the contralateral radial nerve with supramaximal shocks 0.1 msecs. in duration at a rate of 1 per second.

MAJOR FINDINGS

The fact that cortically applied atropine augments the amplitude of evoked cortical potentials was amply confirmed as was the fact that this effect takes quite a bit of time to become maximal even after the atropine has been removed from the cortical surface. However, after this effect of atropine had reached a plateau it was found that further application of prostigmine and acetylcholine produced a still greater augmentation of the size of the evoked responses. Thus the question raised by Dr. Marshall has been answered in the negative.

It was further found, contrary to certain assumptions previously made by Chatfield and Purpura that 10% atropine had an even quicker action than the 2% solution. This finding together with the slow course of action of the atropine indicates that it has its action in deeper layers of the cortex. The results fit the hypothesis previously formulated by Chatfield and Purpura that atropine augments cortical electrical activity by blocking a cholinergic inhibitory system whose final pathway at least involves intra-cortical neurones.

SIGNIFICANCE OF THE PROGRAM TO THE INSTITUTE

Since the pharmacological actions of these drugs as used are essentially convulsive the project can be related to the problem of epilepsy with which the National Institute of Neurological Diseases and Blindness is so concerned. In addition it had a more fundamental significance with regard to cortical physiology in general, and the possible existance of neurohumoral synaptic transmission in the central nervous system.

PROPOSED COURSE OF PROJECT

This phase of the project is complete and it is being documented in a manuscript in preparation. It is planned that the next phase will concern itself with a search for the cerebral mechanism which we believe exerts a tonic inhibitory effect on cortical function, which is blocked by atropine and which is cholinergic in nature. Initial investigations will be devoted to the effects of topically applied atropine on the cortical inhibition which has been reported to result from stimulation of the caudate nucleus (Gerebetzoff 1941).

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-10(C)
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$5,500	1	2	3	0.2	0.8	1.0	
FY 1956	$5,775	1	2	3	0.2	0.8	1.0	

12. BUDGET ACTIVITY:

RESEARCH /X/ ADMINISTRATION

REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. IF WITHIN NIH)

R.F.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-10(C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness (INSTITUTE) 2. Medical Neurology (LOCATION OR BRANCH)

3. Clinical Neurophysiology (SECTION) 4 (LOCATION) 5 NINDB-11(C) (SERIAL NO.)

6. Investigation of the possible origin of muscle cramps.
PROJECT TITLE

7. Forbes H. Norris, Jr., (Guest Worker)
PRINCIPAL INVESTIGATOR

8. Edgar L. Casteiger (Harvard Medical School), Paul O. Chatfield, M.D.
OTHER INVESTIGATOR(S)

9. PROJECT DESCRIPTION

OBJECTIVES

This study was undertaken in order to investigate the origin of muscle cramps since it has not definitely been established whether they are initiated within the muscle itself, in peripheral nerve or in the central nervous system.

METHODS EMPLOYED

Muscle action potentials during voluntary contraction, during reflex activity and during cramps were recorded with microelectrodes, suitably amplified and photographed on a cathode ray oscilloscope.

PATIENT MATERIAL

Studies were made on patients of the National Institute of Neurological Diseases and Blindness, with various neuromuscular disorders and on suitable patients from other Institutes of the National Institutes of Health as well as on normal human volunteers.

9. PROJECT DESCRIPTION, Cont'd.

MAJOR FINDINGS

"Night cramps" occurred in 16% of 115 healthy young students, confirming the findings of previous investigators. Some normal subjects were able to induce cramps at will by maximum voluntary effort, while the muscle was in a position of maximum shortening. This proved useful in studying cramps in the laboratory. All the action potentials recorded were caused by activity of motor units. The motor unit activity during cramps was similar to that recorded in activity of known spinal origin. Spinal reflexes were effective in evoking cramps and in changing their severity.

It is concluded that cramps commonly originate in transient motor hyperactivity of the spinal cord. Less frequently, similar phenomena may arise from disorders of peripheral nerve and muscle. Stretching cramped muscles is effective in abolishing most cramps. It is suggested that preventive treatment of cramps be directed toward suppression of central motor hyperexcitability by use of drugs or restoration of electrolyte balance.

SIGNIFICANCE OF THE PROGRAM TO THE INSTITUTE

Muscle cramps occur frequently in patients of the National Institute of Neurological Diseases and Blindness and until their site of origin is established a rational treatment for their alleviation or prevention could not be developed.

PROPOSED COURSE OF PROJECT

This project is regarded as being completed. A manuscript describing the results is in preparation.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-11(C)
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$5,500	1	3	4	0.3	0.7	1.0	
FY 1956	$5,775	1	3	4	0.3	0.7	1.0	

12. BUDGET ACTIVITY:

RESEARCH /X/ ADMINISTRATION /__/

REVIEW & APPROVAL /__/ TECHNICAL ASSISTANCE /__/

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. IF WITHIN NIH)

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-11(C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness (INSTITUTE) 2. Medical Neurology (LOCATION OR BRANCH)

3. Clinical Neurophysiology (SECTION) 4. _____ (LOCATION (IF OTHER)) 5. NINDB-12(C) (SERIAL NO.)

6. Clinical electromyography with a microelectrode technique

7. Forbes H. Norris, Jr. (Guest Worker)
PRINCIPAL INVESTIGATOR

8. Paul O. Chatfield, M.D., Marvin Korengold, M.D.
OTHER INVESTIGATOR(S)

9. PROJECT DESCRIPTION

OBJECTIVES:

The usual methods of electromyography such as the use of skin or concentric needle electrodes have not proven to be of too great diagnostic or investigative usefulness. By the use of electrodes with a recording area of about 100 square mu inserted into the muscles of normal controls and of patients with various neuromuscular disorders a clearer picture of the normal or pathological physiology can be obtained.

METHODS EMPLOYED

Fine wires insulated except at the tip are inserted into the muscle to be studied, through hypodermic needles which act as cannulae which are taped to the skin to avoid movement artefact. The muscle action potentials picked up between two of these electrodes are suitably amplified and photographically recorded by means of a cathode ray oscilloscope. This procedure is naturally employed under sterile conditions.

PATIENT MATERIAL

The patients used were those being studied by the National Institute of Neurological Diseases and Blindness as well as occasionally patients of interest from other Institutes of the National Institutes of Health.

9. PROJECT DESCRIPTION, Cont'd.

MAJOR FINDINGS

Following prolonged strong contraction, muscles of patients with progressive muscular dystrophy showed electrical activity at rest. This post-contraction activity was due to discharge of hyper-excitable muscle fibers. Some examples of this activity could not be distinguished from fibrillation, and other examples were identical with recordings made during myotonia.

SIGNIFICANCE OF THE PROGRAM TO THE INSTITUTE

This study was part of a more general electrophysiological study of this Institute, seeking information on neuromuscular disorders.

PROPOSED COURSE OF PROJECT

It is planned to use these methods more routinely on patients with neuromuscular disorders in the hope of clarifying the nature of their disease.

A manuscript describing the results of this phase of the investigation is in preparation.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-12(C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$5,500	1	3	4	0.3	0.7	1.0	
FY 1956	$5,775	1	3	4	0.3	0.7	1.0	

12. BUDGET ACTIVITY:

RESEARCH /X/ ADMINISTRATION / /

REVIEW & APPROVAL TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. IF WITHIN NIH)

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-12(C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

R. P. C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness (INSTITUTE) 2. Medical Neurology (LOCATION OR BRANCH)

3. Clinical Pharmacology (SECTION) 4. _____ (LOCATION (IF OTHER)) 5. NINDB-13(C) (SERIAL NO.)

6. Neuromuscular and Ganglionic Blocking Agents: Central nervous system affects. (PROJECT TITLE)

7. Richard L. Irwin, Ph.D. (PRINCIPAL INVESTIGATOR(S))

8. Jay B. Wells, M.S. (OTHER INVESTIGATORS)

9. PROJECT DESCRIPTION

OBJECTIVES: The objective of this project was to develop a method to compare the peripheral and central effects of the neuromuscular and ganglionic blocking agents and to determine these effects for clinically useful compounds.

METHOD EMPLOYED: A cross circulation preparation using two dogs in which the head of one dog is vascularly isolated from body and the brain is perfused by blood from another dog. Vascular isolation of the head is confirmed by a photometric method using the dye T1828.

MAJOR FINDINGS: The major findings of this project during the past ten months have been:
(1) The development of a cross circulation method that vascularly isolates the head and leaves neural connections intact.
(2) The neuromuscular blocking agents, d-tubocurarine, succinylcholine and decamethonium that are in clinical use have been shown to have no central respiratory action as has been previously reported.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: In order that clinically useful drugs may be administered other than on an empirical basis a greater understanding of this mode of action is imperative. The knowledge of how a given drug produces

its observed effect thus benifits the patient and increases the safety with which it can be administered. During the time the neuromuscular blocking compounds have been in clinical use, prolonged respiratory arrest has been observed following the use of these substances during anesthesia. The prolonged apnea has been reported as a central depressant action on the respiratory center. The presence of such an effect would increase markedly the hazard of use of these compounds for the patient. The clinically and fundamentally important question of whether the neuromuscular blocking agents in clinical uses are centrally depressant to respiration is difficult to evaluate since the end effect of a central or peripheral action would be identical. This project has to date been concerned with the development of an adequate method to compare the central and peripheral respiratory effects of the neuromuscular blocking compounds and a comparison of these effects for the clinically important d-tubocurarine, succinylcholine and decamethonium.

PROPOSED COURSE OF PROJECT: The part of the present project concerned with the neuromuscular blocking agents is essentially completed. The investigation into a comparison of the central and peripheral effects of the ganglionic blocking agents will be continued utilizing the isolated head technique that has been developed. An extension of the present method to the investigation of the site of action of other clinically or fundamentally important drugs is proposed.

Budget Data Sheet

10. NINDB-13(C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	
FY 1955	$8,550	1	2	3	0.5	1.0	1.5	
FY 1956	$9,300	1	2	3	0.5	1.0	1.5	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956; IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM)

NONE

14. IF THIS PROJECT RESEMPLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHFRE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUDNS), IDFNTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

NONE

Honors, Awards, and Publications Sheet

15. NINDB-13(C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROMTHIS PROJECT DURING CALENDAR YEAR 1954:

NONE

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

Project Description Sheet

1. Neurological Diseases and Blindness (INSTITUTE) 2. Medical Neurology (LABORATORY OR BRANCH)

3. Clinical Pharmacology (SECTION) 4. _____ (LOCATION (IF OTHER)) 5. NINDB-14(6) (SERIAL NO.)

6. Neuromuscular blocking agents: Peripheral action related to Calcium, Potassium, Carbon dioxide and Anoxia. (PROJECT TITLE)

7. Richard L. Irwin, Ph.D. (PRINCIPAL INVESTIGATOR(S))

8. Jay B. Wells, M.S. (OTHER INVESTIGATORS)

9. PROJECT DESCRIPTION:

OBJECTIVES: The objective of this project is to determine how changes in ionic concentrations and respiratory gases affect the neuromuscular block produced by the clinically useful neuromuscular blocking compounds.

METHODS EMPLOYED: The effect of ions on a neuromuscular block has been determined by a method developed during the course of the project. The experimental animal is denitrogenated and maintained in an oxygen atmosphere and the duration of action of the drug is measured under various experimental conditions. The effects of changes in respiratory gas concentration are measured by means of a gastroenemius sciatic nerve muscle preparation in the rat.

MAJOR FINDING: The major finding of this project during the past nine months is that an infusion of calcium significantly decreases the duration of apnea induced by succinylcholine. A method has been developed that makes possible the measurements the effects of ions on a neuromuscular block in absence of extraneous electrical stimulation and artificial respiration. This method more nearly approximates the conditions under which these drugs are administered than previous methods.

NINDB-14(C)
SERIAL NO.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: Myasthenia Gravis and familial periodic paralysis are neurological diseases in which both a deregement of neuromuscular transmission and changes in ionic concentration in the blood may be involved. Until more knowledge on the mechanisms of a neuromuscular block and its relation to ionic concentration is available the etiology and treatment of these diseases must necessarily remain empirical. It is therefore important to examine the phenomena of neuromuscular block in greater detail than is possible in the patients. The investigation of the neuromuscular block and the conditions which affect it is the problem with which this project is concerned.

PROPOSED COURSE OF PROJECT: A portion of the next calendar year will be devoted to the continued investigation of the effects of ions on the phenomenon of neuromuscular block with emphasis on potassium and calcium The general approach to the problem will be based on in vitro as well as in vivo studies. The investigation of the effect of the respiratory gases on a neuromuscular block will be continued.

Budget Data Sheet

10. NINDB-14(C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS		
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL
FY 1955	$8,550	1	2	3	0.5	1.0	1.5
FY 1956	$9,300	1	2	3	0.5	1.0	1.5

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATION UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM)

NONE

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTER* CHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

NONE

Honors, Awards, and Publications Sheet

15. NINDB-14(C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

Analysis of NIH Program Activities

Project Description Sheet

1. N.I.N.D.B. — INSTITUTE
2. Medical Neurology — LABORATORY OR BRANCH
3. Clinical Neurochemistry — SECTION
4. [illegible] — LOCATION
5. NINDB-15 (C) — SERIAL NO.

6. Glutamine and Glutamic Acid Metabolism in Normal and Epileptogenic Cerebral Cortex.
PROJECT TITLE

7. Dr. Donald B. Tower
PRINCIPAL INVESTIGATOR

8. Dr. Maitland Baldwin, Dr. C. Ajmone-Marsan, Dr. Ellsworth Alvord
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(a) Objectives of this project are to study the in vitro metabolism of glutamine and glutamic acid by slices of cerebral cortex from (1) human patients operated for focal epileptogenic cortical lesions and (2) experimental animals.

(b) Methodology: Human cortical samples are obtained from patients during surgery for excision of epileptogenic foci, each sample being rated by established criteria in cooperation with the neurosurgeon and the electroencephalographer. Animal samples are obtained primarily from cats, either normal or with seizures experimentally induced by methionine sulfoximine. Where possible samples for histological control are taken and prepared by the neuropathologist. All cortical samples are sliced fresh to an optimal thickness of 0.5 mm. with a Stadie-Riggs microtome in a humid chamber. Slices are weighed on a torsion balance and placed in Warburg vessels containing a nutrient salt medium buffered with bicarbonate and containing glucose, so constituted that it closely resembles natural brain interstitial fluid. The vessels are gassed with an optimal mixture of 95% oxygen - 5% carbon-dioxide and incubated at body temperature (37° C) on a Warburg bath. Most slices are incubated with increased concentrations of potassium (27 mM) in the medium, which in effect places a work load on the tissue analogous to that during neuronal activity in vivo. Some normal animal slices are incubated with only 10% oxygen in the gass mixture, a procedure which has been shown to reproduce or mimic certain defects in metabolism exhibited by epileptogenic tissue. Metabolites, drugs or other agents under study are added to incubating slices in order to observe

their effects on metabolism. By this technique non-epileptogenic or normal slices and epileptogenic slices are studied under identical conditions so that their relative capacities to carry out metabolic work can be directly observed. At the end of a standard incubation period (60 min.) the slices and media are separated by filtration, the slices homogenized and both slices and medium samples preserved at an acid pH.

The total content of glutamine plus glutamic acid in each sample is determined microbiologically, using suspensions of gas bacillus (Clostridium welchii) which contain a specific glutamic decarboxylase, so that the measurement on the Warburg apparatus of the carbon-dioxide released during the reaction is equivalent to the total glutamic acid and glutamine present. Since the bacilli also deamidate glutamine, aliquots of the mixture are then analyzed for ammonia by subjecting the aliquot to Conway microdiffusion and determining the ammonia content by the Russell alkaline phenol-hypochlorite reaction. Subtraction of the amide ammonia values (glutamine fraction) so obtained from the total carbon dioxide values gives the glutamic acid fraction. By using sets of slices removed at the start of incubation and comparing their levels with those of slices incubated 60 minutes, the change in glutamine and glutamic acid levels is obtained.

(c) Patient material is obtained from NINDB patients admitted to the Surgical Neurology branch and operated on for excision of focal epileptogenic cortical foci. Since some of these excisions require removal of overlying or adjacent uninvolved cortex, a small number of non-epileptogenic samples is being accumulated.

(d) Major findings: Studies during calendar 1954 have confirmed preliminary experiments, demonstrating a definite defect in the metabolism of glutamic acid by epileptogenic cerebral cortex. This defect is a significant and chronic defect which is characterized by a "metabolic loss" of glutamic acid during incubation of epileptogenic slices. This loss contrasts with an increase in glutamic acid found in non-epileptogenic or normal slices, and the loss clearly is not a loss to the exterior of the slices but is an abnormal utilization of glutamic acid by metabolic systems of the tissue. Representative figures are:

Sample	Tissue Glutamic Acid Level	Change	Tissue Glutamine Level	Change	Glutamine initially diffused into Medium Level	Change
Non-Epileptogenic						
Initial	7.85		4.0		4.3	
60 Min.	9.3	+1.45	5.0	+1.0	2.05	-2.25
Focal Epileptogenic						
Initial	6.25		3.7		4.8	
60 Min.	4.75	-1.5	5.35	+1.65	3.35	-1.45

Since the uptake of glutamine from the incubation medium and the rise of glutamine in the slices are comparable in both types of samples, the defect appears to involve glutamic acid directly.

It has now been clearly demonstrated that the defect in glutamic acid metabolism is not a structural or irreversible defect but a functional defect which can be reversed by the in vitro addition of asparagine, adenosine triphosphate (ATP), α-ketoglutarate or pyridoxal phosphate but not by simple amides such as valeramide or acetamide. The effective agents are all presumably concerned in the complex transamination reactions by which glutamic acid and α-ketoglutarate effect interchange with each other in tissue metabolism to permit carbohydrate and amino acid metabolism to interlock effectively. Glutamic acid plays a central role at this metabolic cross-roads and because of its high concentration in nervous tissue it is thought to be an active and essential constituent for normal neuronal function and activity. Interference with its metabolism, demonstrated here for the first time, suggests that it may be intimately concerned with seizure mechanisms. Previous experimental evidence of several types supports this view. In addition results in other projects of this section (clinical trials of asparagine and glutamine and defects in electrolyte metabolism of cortical slices) also support this view.

Experimental animal studies have resulted in an apparent reproduction of some aspects of this defect in glutamic acid metabolism and shed some light on the nature of the defect. Normal cortical slices incubated with 10% oxygen (instead of the usual 95%) lose glutamine to the incubation medium during incubation and the glutamic acid level in the slice falls. Critical examination of these results indicate that glutamic acid or glutamine is being produced by the slice, presumably from carbohydrate sources via α-ketoglutarate, in an attempt to maintain tissue levels in the face of an external drain. This finding is consonant with theories which consider carbohydrate as the main source of glutamic acid in brain under normal metabolic conditions rather than actual delivery of glutamic acid per se to the tissue. In cortical samples from animals in which seizures are induced with methionine sulfoximine, there is an absence of glutamine (confirming previous work on the toxicity of this agent for glutamine

synthesis) but also a low level of glutamic acid which falls during slice incubation. This finding suggests, but does not prove, that glutamine must be present or able to be formed to maintain glutamic acid levels in the slice. When these observations are applied to the situation in human epileptogenic cortex, the concept that glutamic acid is not being formed or maintained but is being used up by the tissue may be explicable in terms of an interference in energy production or utilization from carbohydrate. It is a logical working hypothesis therefore to consider that correction of the defect may be achieved by external supply of glutamic acid (as its diffusible form glutamine) or by replacement with a closely related amide, asparagine. Successful seizure control in patients by use of glutamine or asparagine does not prove these points but is suggestive evidence in the direction of confirmation.

The route by which glutamic acid is being metabolized is under investigation in these slice preparations. Preliminary results indicate that γ-aminobutyrate, which is an intermediate in one major pathway, is also low in epileptogenic cortex. This is consonant with low glutamic acid as a source for this reaction and shows that there is no buildup of γ-aminobutyric acid during the metabolism of glutamic acid by the tissue. It does not obviate the possibility that the reaction proceeds through this pathway although this appears less likely than the direct conversion of glutamic acid to α-ketoglutarate.

(e) Significance of this project: Since seizures are a major concern of NINDB as well as a major neurological problem to the population in general, knowledge of the mechanisms underlying them are essential for development of better and more rational therapy. More fundamentally, knowledge of seizure mechanisms will provide many of the factors which are concerned with neuronal function and activity in general and thus be basic to many problems of neurophysiology and neurological diseases. The defect in glutamic acid metabolism in human epileptogenic brain tissue is one of several components of a biochemical lesion of this tissue, which represents the first such lesion of a major neurological disease to be uncovered.

(f) Proposed course of project: Continuation of present studies is actively underway to complete the data now in hand and to extend the studies to determine, if possible, the routes of the metabolic loss of glutamic acid. Completion of present data will require assessment of the effects of anticonvulsant drugs, lower potassium concentrations and other agents on glutamic acid metabolism. The second phase will be pursued by conventional analyses of known reaction products as well as use of isotopically-labelled constituents to follow the course of such reactions. The dynamic nature of many of the metabolic systems concerned require the use of isotope tags since intermediates and alternate pathways are readily missed when tagging is not done.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-15 (C)
SERIAL NO.

11.

11. BUDGET DATA:

FY	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
1955	$25,000	1	2	3	0.3	0.2	0.5	*
1956	$27,200	1	2	3	0.3	0.2	0.5	*

* Patient material used in derived from patients admitted to other NINDB projects.

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

Research and Development Divisions, Merck & Co., Inc.
Research Division, Wallace & Tiernan Co., Inc.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-15 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Tower, D. B. "The Neurochemistry of Seizures" in Current Research in Neurochemistry and Allied Fields, Edited by S. R. Korey and J. I. Nurnberger; New York, Paul B. Hoeber, 1955. In Press.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None.

Analysis of NIH Program Activities

Project Description Sheet

1. N.I.N.D.B. — INSTITUTE
2. Medical Neurology — LABORATORY OR BRANCH
3. Clinical Neurochemistry — SECTION
4. ____ — LOCATION (IF OTHER THAN BETHESDA)
5. NINDB-16(C) — SERIAL NO.

6. Clinical Evaluation of the Value of Glutamine or Asparagine for the clinical control of Seizures.
PROJECT TITLE

7. Dr. Donald B. Tower
PRINCIPAL INVESTIGATOR

8. Dr. Charles E. Wells, Dr. C. Ajmone-Marsan
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(a) Objectives of this project are to study the effectiveness of two naturally-occurring amino acid amides, L-asparagine and L-glutamine, in controlling seizures in epileptic patients and to observe their effects on epileptiform activiy in the electroencephalogram of suitable patients. This project had its inception in the findings on human epileptogenic cortex in vitro that significant, chronic defects in metabolism of acetylcholine, glutamic acid and electrolytes occur which can be reversed by addition in vitro to such tissue of either glutamine or asparagine, neither of which appear to affect normal in vitro metabolism nor to exhibit any effects when administered in large quantities in vivo to normal subjects.

(b) Methodology and Patient material: Patients for this project have been obtained either from those admitted to the medical or surgical neurology branches or by direct referral from outside physicians. Criteria for admission to the project were set up as follows: (1) Reliable history of seizures confirmed by electroencephalography, with poor control on standard anticonvulsant regimes, (2) Frequent clinical seizures both by history and by ward observation at NIH, limiting suitable cases to those with a frequency of at least several seizures per week and usually daily, and (3) if possible, EEG abnormalities which are consistent, constant and reproducible enough for assessment of changes. Thus, problem cases with severe degree of involvement and poor control on adequate medication regimes have been selected exclusively. No limitations in regard to age, sex or type of seizure have been placed. The only limitation set has been the exclusion

of patients with evidence of hepatic, renal or cardiovascular disease because of the dose and nature of compounds being assessed.

All patients have been admitted to the NINDB ward service for observation of seizure frequency and for frequent EEG's during a period of not less than 3 weeks, usually 4-5 weeks. Routine neurological work-ups and laboratory tests, including renal and hepatic function tests, are carried out during this period. In general previous medication is maintained unchanged both to avoid complicating the assessment of results on trials of the new agents and to avoid precipitating loss of what seizure control already exists.

During this period patients with suitable EEG abnormalities on repeated recordings may receive glutamine or asparagine or both intravenously in a dose of 2-3 mM/kg. body weight during EEG recording. The results of these studies are assessed with the electroencephalographer.

If no contraindications develop, patients are then started on daily oral doses of glutamine or asparagine or a combination of the two. Dosages, so far empirically determined on experimental in vitro evidence, are 2-3 mM/kg. body weight each given 4 to 6 times daily. Patients are retained on the wards for 3-6 weeks longer to permit dosage adjustment and continuation of seizure frequency observation, EEG recordings and laboratory examinations. Patients are then discharged home on medication and report monthly on standard seizure and medication record forms (PMS-1989) together with laboratory data as required. Each patient returns to the Follow-up Unit or is admitted briefly to the ward for checks on progress at intervals of 2-4 months. In each case a trial for at least one year is being carried out whenever possible.

Intravenous preparations of the amides are sterile and pyrogen-free. The asparagine is made up as a stanrdard 4.5% i.v. solution. Owing to its instability in solution or on autoclaving, glutamine has been prepared for i.v. use in ampoules in a lyophilized form by Merck & Co. and has proven most satisfactory in this form. Oral administration of the relatively large quantities of material remains a problem in bulk. The asparagine is now being formulated by Merck & Co. as a flavored 25% suspension, which has proven to be quite satisfactory except for the bulk of supplies required(15-30 bottles per month). The development of synthetic L-glutamine of high purity (99%) has made it possible to start trials of this also. It is used in powder form, each dose being dissolved in a glassful of juice, milk or water at the time of administration. Because of its instability formulation of glutamine into suspensions has not been adopted.

(c) Major Findings: A total of 29 patients have been or are now being studied in this project. Of these 5 represent preliminary patients or subjects no longer actively under therapy. The 24 active patinets can be tabulated in the following manner:

Table I

	D-asparagine	L-glutamine	Both	Totals
Total Patients on Oral Therapy	16	5	3	24
Male	10	4	3	17
Female	6	1	0	7
6-14 Yrs	7	4	0	11
16-40 Yrs	9	1	3	13
I.V. Studies	2	4	(2)*	6
Duration of Oral Therapy				
Total Patients	16	5	3	24
Over 12 mos.	2	0	0	2
9-12 mo.s	0	0	0	0
6-9 mos.	2	0	0	2
3-6 mos.	3	2	0	5
1-3 mos.	2	2	3	7
Less than 1 mo.	7	1	0	8
Preliminary Results				
No. patients on therapy at least 2 months	9	4	1	14
Essentially seizure free	3	0	0	3(20%)
60% or more reduction in Seizures	5	3	1	9(65%)
Equivocal Response	1	1	0	2(15%)

*
(Patients who received both amides i.v., each on separate occasions.)

All types of seizures (major, minor or petit mal, and focal) are represented in this group with the exception of the rare myoclonic type (and this has been studied elsewhere in co-operation with NINDB). So far no distinction has been apparent in the response seen for the various types, all responding well in the majority of cases. Most of the patients experience seizures only during waking hours, but several patients have exclusively nocturnal seizures which also have responded satisfactorily. On the basis of Table I it is estimated that over 80% of patients observed for 2 months or longer have experienced a significant reduction in seizure frequency Since these are all severely involved patients, it could not necessarily be expected that many would be rendered seizure-free. However, one patient on asparagine alone and one on asparagine added to other medication have remained essentially seizure-free for one year and almost nine months respectively. For other patients it has been possible to reduce other medications or omit them entirely with maintenance of improvement attained after starting amide therapy. In addition general improvement has been noted in almost every case, such as greater alertness, improved skilled movements, intellectual advancement, and fuller or more normal social life. In the younger age group several patients previously unable to continue schooling have been able to resume schooling and to make good progress, and one boy has been apparently saved from institutionalization. In the older age group patients previously unable to work because of seizures have now been able to secure and maintain gainful employment. While this group is still small in number and has been studied in most cases less than 6 months, the results appear to be highly encouraging both from a clinical and from a socio-economic standpoint.

Several subsidiary observations deserve comment. As studies have progressed, it has become apparent that the dosage of asparagine or glutamine is not as arbitrary as its original basis would imply. In suitable patients stopping therapy has resulted in reversion to previous poor control and re-institution of amide therapy has achieved control again. Without placebo studies such results must be interpreted cautiously. In patients with very frequent minor or petit-mal seizures (20 or more daily) it has become apparent that either higher dosage or probably more frequent doses are required to achieve satisfactory reduction in seizures. Doses less than 2 mM/kg. body weight in several cases have been ineffective until increased to at least that amount. Preliminary studies of blood levels and in one case spinal fluid levels indicate that significant elevation of serum amide levels occurs and that a level in the spinal fluid is apparently achieved which is close to the concentration of 2 mM/kg. being aimed for. Electroencephalographic studies of patients on oral therapy have not in general shown significant changes, a result in keeping with previous observations that good clinical control may be attained with a variety of anticonvulsants without materially affecting EEG

abnormalities. However, several patients have shown definite EEG improvements after institution of amide therapy. Full assessment of this phase of the project has not yet been undertaken. Many of the patients have now consumed kilograms of amide, some for over 12 months, and so far no toxic or side effects have been observed or reported despite continued careful laboratory checks. The safety of administering such relatively large doses of these naturally-occurring amides seems to be well established.

(d) Significance of this project would seem to be self-evident. It represents a new type of compound which has definite anticonvulsant properties, but which differs from all other anticonvulsants not only in its chemistry but in its lack of toxicity and lack of sedative or hypnotic action. It represents development of therapy based on a demonstrated biochemical lesion in human epileptogenic brain tissue. The number of problem cases referred to NINDB or contained in inquiries from neurologists and physicians in this country and abroad indicate that better, more effective therapy for seizures is in demand. With over a million and a half seizure patients in this country alone, it is a major health and economic concern. In addition this project is representative of the type of research for which the clinical investigation phases of NIH were created in that it has taken laboratory findings, applied them to patient material at the Clinical Center in a detailed manner seldom possible elsewhere, developed agents of considerable initial cost to the point where cost is being lowered to more reasonable ranges, and promoted trials elsewhere (as noted below).

(e) Proposed Course of the project is to continue the studies underway, adding more patients to a total of about 35 and continuing patients now under therapy. Several aspects of the project will be considered in more detail, including the role and effect of Vitamin B_6 (pyridoxine), which acts as a coenzyme for metabolism of amino acids and their amides, and also the effectiveness of racemic DL-asparagine compared to natural L-asparagine. The latter is important from a long-term standpoint since DL-asparagine can be easily and inexpensively synthesized, but L-asparagine would be difficult and expensive to make synthetically.

 Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-16 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$300,000	2	2	4	0.8	0.4	1.2	1355*
FY 1956	$175,000	2	2	4	0.8	0.4	1.2	1000 est

* Actual total for calendar year 1954.

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

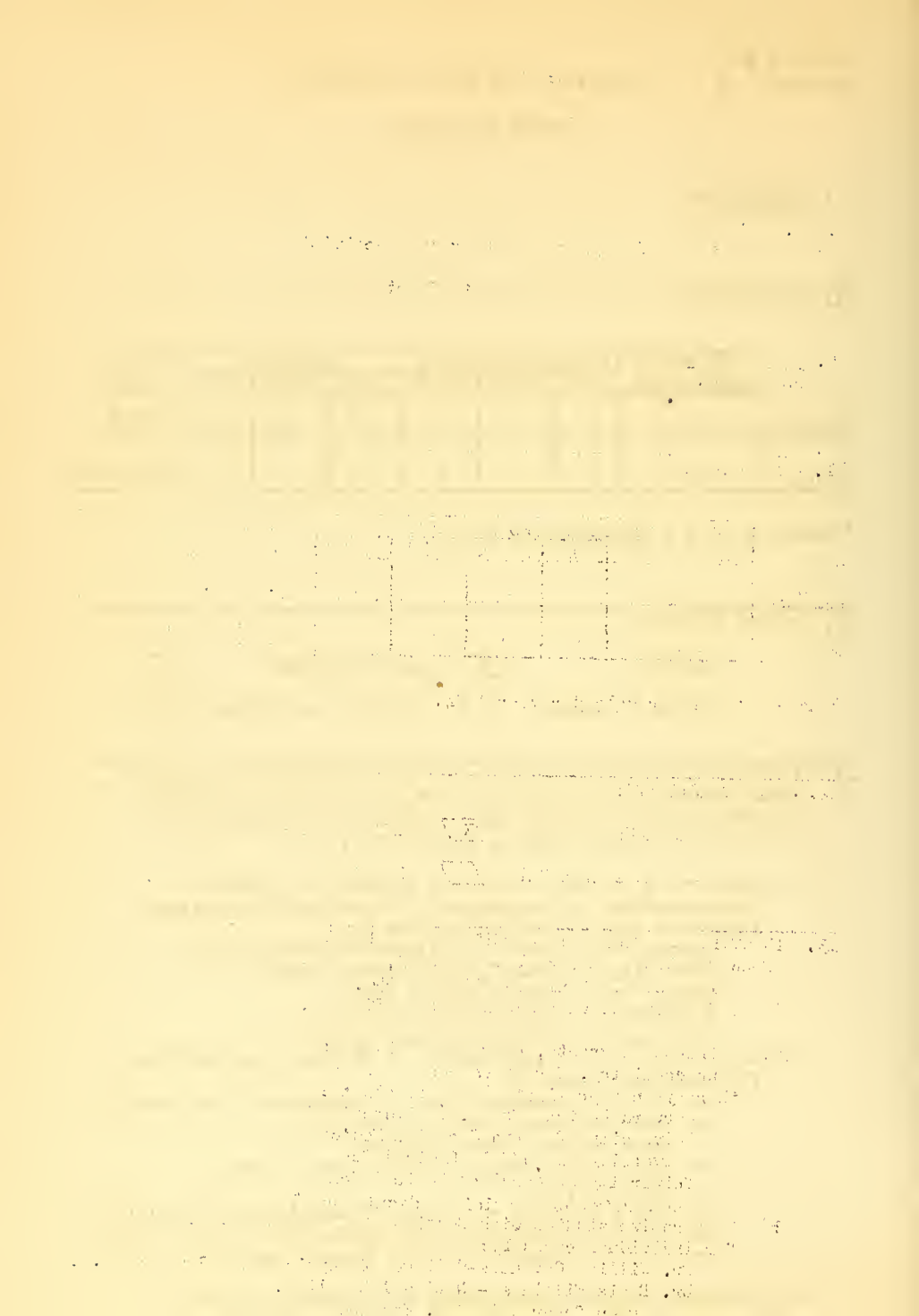
REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1).

(a) Extra-mural grants, coordinated by Section of Clinical Neurochemistry, for assessment of L-asparagine in seizure therapy on approximate 100 patients to:
Harvard Medical School (Children's Medical Center)
University of North Carolina Medical School
University of Buffalo Medical School
University of Maryland Medical School
University of Virginia Medical School

(b) Cooperative studies with Section of Clinical Neurochemistry for individual cases by:
Dr. William Caveness-College of Physicians & Surgeons,N.Y.
Dr. Denis Williams - National Hospital, Queen Square, London, England
Dr. Irwin Levy - Washington Univ. Medical School, St. Louis, Mo.
Dr. Hudson Hoagland - Worcester Foundation, Worcester,Mass.
Dr. Saul Korey-Western Reserve Medical School,Cleveland, O.
Dr. Louis Goodman-Univ. of Utah Medical School

(c) Research and Development Divisions, Merck & Co., Inc.



14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

None.

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-16 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Tower, D. B. "The Nature and Extent of the Biochemical Lesion in Human Epileptogenic Cerebral Cortex and an Approach to its Control in vitro and in vivo.

Neurology 5: (Feb. 1955) In Press.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None.

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Medical Neurology — LABORATORY OR BRANCH
3. Clinical Neurochemistry — SECTION
4. LOCATION(OTHER THAN BETHESDA)
5. NINDB 17(C) — SERIAL NO

6. Metabolism of Glutamic and Aspartic Acid Amides in vivo. — PROJECT TITLE

7. Dr. William C. Curtis and Dr. Donald B. Tower — PRINCIPAL INVESTIGATOR(S)

8. Dr. Charles B. Wells and Mr. Donald Cummings — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

OBJECTIVES: Of this project are to develop suitable clinical methods for simultaneous quantitative determination of glutamic acid, aspartic acid, glutamine and asparagine in body fluids (blood, cerebrospinal fluid, urine) in order to follow the metabolic rate of ingested doses of glutamine or asparagine or both in seizure patients on such therapy and to correlate such findings with oral dosage and clinical response.

METHODS EMPLOYED: Samples of blood plasma, deproteinized with tungstate or metaphosphoric acid, or standard solutions containing the amino acids in question, are treated with chloro dinitro benzine by the method of Sanger to form the dinitrophenyl-derivatives of all amino compounds present. The mixture is brought to pH 5 and transferred to a celite column, which retains only the derivatives of serine, threonine, glutamic acid, aspartic acid, glutamine and asparagine at that pH, passing all other amino acid derivatives and artefacts through. The bands are eluted separately by using varying concentrations of chloroform and ether, the order of elution being (1) glutamic acid, (2) glutamine, (3) threonine, (4) serine, (5) aspartic acid, and (6) asparagine. The band fractions eluted are evaporated to dryness and redisolved in 1N hydrochloric acid. The yellow solution is then ready quantitatively by spectrophotometer at 340 mμ. This method has been found previously to be sensitive to 1-10 micrograms per sample of amino acid derivative.

Where radioactive carbon - 14 labelled asparagine or glutamine is employed, analyses are carried out using paper chromatography in two dimensions on Whatman #1 paper with phenol and lutidine respectively as solvents. Identification of amino acid spots with Ninhydrin reagent is made and the carbon - 14 activity of the spots counted with a pre-flush, geiger-type counter, supplemented by

radioautographs.

Studies on patients and human control subjects (if necessary) are done in two ways. A type of amide "tolerance" curve is done in which fasting blood and spinal fluid samples are drawn before an ingested dose of glutamine or asparagine and subsequent samples are drawn at appropriate intervals thereafter (for blood plasma, usually 30, 60, 120, 180 and 240 minutes). In addition daily levels in blood and possibly spinal fluid will be taken on patients on regular daily oral therapy. Complete metabolic studies will be attempted where urinary determinations have been more fully investigated. Correlations of these data with blood NPN and BUN levels and urinary urea and ammonia are contimplated.

Experimental animal studies will be carried out using the above methods and in addition will be done with tracer amounts of carbon - 14 tagged amides. This latter study is designed to follow the course of ingress of the amides into the central nervous compartment and into central nervous tissue which will be biopsied through previously placed burr holes. Monkeys will be used primarily for this study, although preliminary studies in cats will also be carried out. The use of isotopically labelled amides will also permit study of the direction and course of metabolism of these amides after entry into the blood, spinal fluid and brain.

PATIENT MATERIAL: will be derived from the patients being studied in the clinical study assessing the anticonvulsant effectiveness of glutamine and asparagine (Serial # 16C). Other NINDB patients not on such therapy will be used for acute studies.

MAJOR FINDINGS: Although this project was begun only three months ago, the dinitrophenyl method has been developed to the point of clinical application. No previous publication has been found in which simultaneous determination of the four closely related amino acids, glutamine and aspartic acid and glutamine and asparagine, has been attempted or achieved. There are two other methods for glutamic acid and glutamine determinations which though tedious can be used, but no method for asparagine or for the four simultaneously has apparently been developed for clinical application. Despite the theoretical attractiveness of this method, it has apparently been avoided because of the difficulty in preparing pure dinitrophenyl glutamic acid with which to standardize the procedure. By starting with pure glutamine, forming its dinitrophenyl derivative and deamidating the product, a satisfactory glutamic acid compound has been obtained. Direct formation has yielded only an oil which will not crystallize. This is a problem in standardization only, since biological samples need not be crystallized before running through the column. A second problem in this regard was met in obtaining pure L-glutamine as starting material, since commercially available natural L-glutamine appears to contain an isomer or closely related derivative which cannot be readily separated (possibly isoglutamine). Purification of

glutamine is in progress as well as trial of synthetic L-glutamine. Purified L-glutamine so far has been kindly supplied by Dr. Alton Meister (NCI).

Preliminary studies by serum NPN levels and glutamine levels (determined by Dr. Meister) indicate that in patients on asparagine or glutamine in oral doses of 2 mM/kg. body weight 4-6 times daily, the fasting level of amide 10-12 hours after the last dose is slightly above the upper limit of normal range. After ingestion of a single dose at this time, the amide level in blood plasma rises to 3-4 times the fasting level with a peak at 1-2 hours and then falls to the fasting level by 3-4 hours. A single cerebrospinal fluid glutamine level 2½ hours after oral dose was about 3 times the average normal for spinal fluid at a level (1.6 mM/litre) very close to that being amid for (2 mM/litre). After a period of time on oral therapy the serum NPN tends to remain elevated significantly above control levels and the BUN rises often significantly. On cessation of therapy both promptly fall to control ranges and rise again when therapy is reinstituted. Thus it is clear in the few patients studied so far that oral dosages of either amide are absorbed promptly from the intestinal tract, producing a significant rise in blood level and apparently also in cerebrospinal fluid level, which lasts about 4 hours. Thus, the dose being used and the dosage intervals would appear to be reasonable on this basis.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: Significance of this project is in the interpretation of results being obtained in clinical therapy with glutamine and asparagine. With the use of any new compound for therapy it is important to being able to determine it in body fluids, to know the course of its metabolism and to be able to correlate dose, body level and clinical effect. With the quantities of amides being administered this becomes even more important.

PROPOSED COURSE OF THE PROJECT: The proposed course of the project is to institute routine studies of body fluids with the dinitrophenyl derivative method and collect data sufficient to answer questions posed above. In addition studies in animals (monkeys) with and without experimentally induced cortical epileptogenic foci (using alumina cream injections) are to be set up both for similar determinations and for use of carbon - 14 labelled amides.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-17 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$29,500	3	3	6	0.5	0.5	1.0	*
FY 1956	$30,000	3	3	6	0.5	0.5	1.0	

* Patient material used is derived from patients admitted for other NINDB projects

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

National Cancer Institute - Dr. Alton Meister
CC Clinical Pathology - Dr. Elizabeth Frame

Research and Development Divisions, Merck and Co., Inc.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH).

None

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-17 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954.

None

Analysis of NIH Program Activities

Project Description Sheet

1. N.I.N.D.B. (INSTITUTE) 2. Medical Neurology (LABORATORY OR BRANCH)

3. Clinical Neurochemistry (SECTION) 4. _____ (LOCATION (IF OTHER THAN BETHESDA)) 5. NINDB-13(C) (SERIAL NO)

6. Electrolyte Metabolism and Energy Metabolism in Normal and Epileptogenic Cerebral Cortex
PROJECT TITLE

7. Dr. Donald B. Tower
PRINCIPAL INVESTIGATOR

8. Dr. Maitland Baldwin, Dr. C. Ajemne-Marsan, Dr. Ellsworth Alvord, Mr. Edmand Peters, and Mr. Donald Cummings.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(a) Objectives of this project are to study the in vitro metabolism of electrolytes, sodium and potassium, and of energy-producing cycles and compounds by slices of cerebral cortex from (1) human patients operated on for focal epileptogenic cortical lesions and (2) experimental animals.

(b) Methodology: The slice technique employed is essentially the same as that outlined in detail in project # NINDB-15(C) entitled "glutamine and glutamic acid metabolism in normal and epileptogenic cerebral cortex," under para. 1 of methodology.

Sodium and potassium levels in incubated slices and media are determined (after filtration separation of slices and media) by lithium -internal standard flame photometry. Since electrolyte concentrations in the incubation medium are high, relative to those in the slice, correction for medium adherent to slices is made by Krebs' method by the weight-gain factor of the incubated slices. Methods for checking the validity of this correction are under study. One is the use of traces of albumen tagged with radioactive iodine-131, which presumably will not penetrate the tissue readily but will label that aliquot of medium actually adherent to the exterior of the slice. The other methods will involve measurement of extra- and intra-cellular spaces in the tissue slice to obtain the true intracellular electrolyte concentrations. These will include measurement of the thiocyanate,

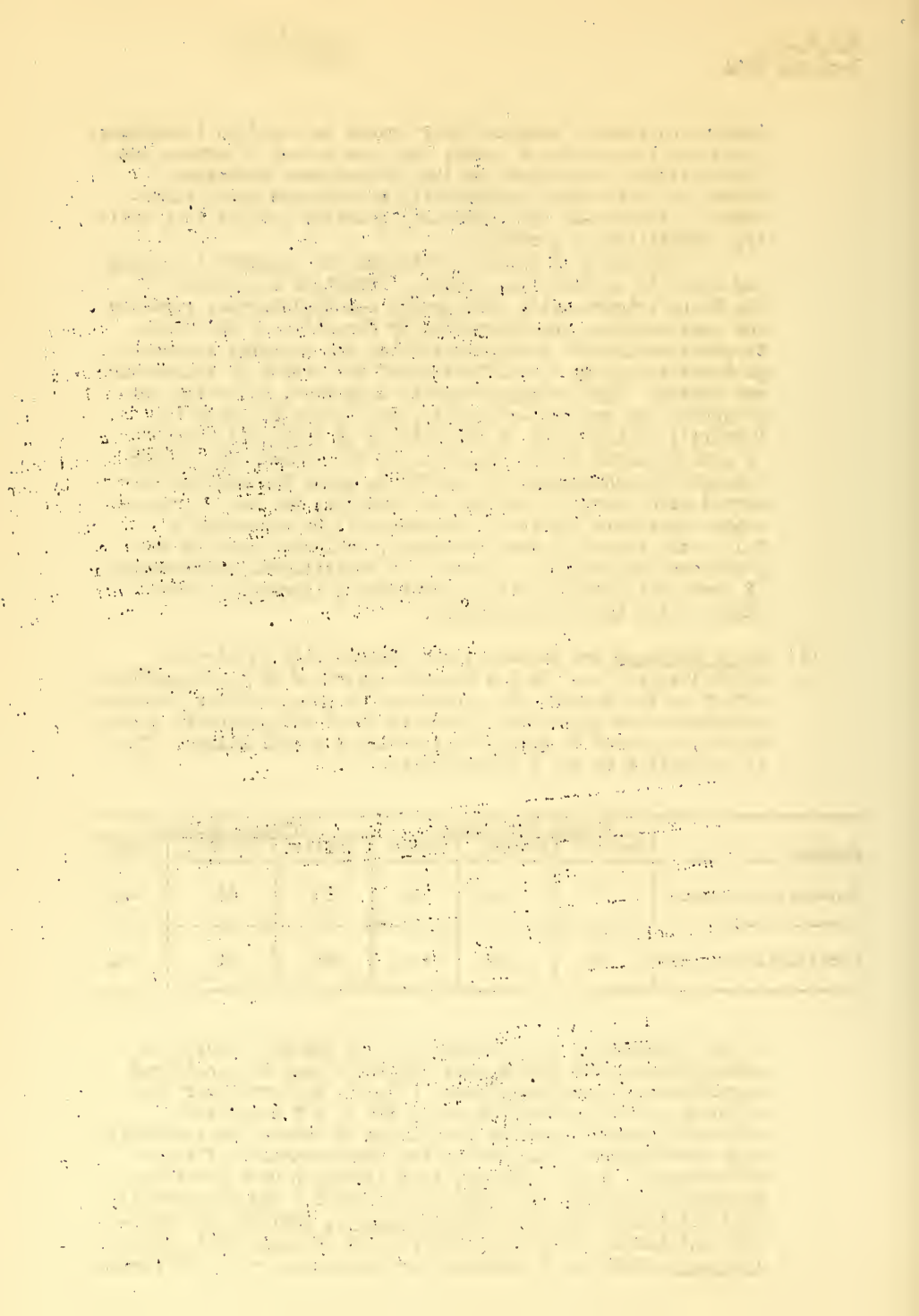
inulin and sucrose extracellular spaces by standard techniques, total and intracellular water, and measurement of extra- and intracellular electrolyte by the Boyle-Conway technique. Sodium and potassium exchange will be measured using radioactive potassium-42 and Sodium-24, counting samples in a well-type scintillation counter.

Components of energy metabolism are measured in slices and media in an analogous manner. Principal components of the Krebs tricarboxylic acid cycle, α-ketoglutarate, pyruvate and oxaloacetate, are determined by formation of the dinitrophenyl-hydrazone derivatives which are measured spectrophotometrically by a modification of the method of Friedemann and Hangen. High energy-phosphate compounds, adenosine triphosphate and creatine-phosphate, are measured either by Umbreit's modification of the methods of Fiske and Subbarow or with specific enzyme preparations from muscle by Warburg manometric techniqures. In addition, since the systems concerned with energy metabolism are dynamic, the use of radioactive carbon-14 labelled compounds will be necessary to follow the course of such reactions, analyzing results with paper chromatographic separation of constituents and counting of carbon-14 activity with a pre-flush geiger-type counter supplemented by radioautography.

(c) Major Findings are principally concerned with electrolye metabolism so far. It has been demonstrated that a significant defect in the uptake and maintenance of intracellular potassium concentrations apparently occurs in human epileptogenic cortical slices, compared to non-epileptogenic or normal slices. This is summarized by the following data:

Sample	Tissue Potassium			Tissue Sodium		
	Initial	60 Min.	Change	Initial	60 Min.	Change
Non-epileptogenic	79	104	+25	86	63	-23
Focal Epileptogenic	69	72	+ 3	95	91	- 4

If the validity of the correctsions for adherent medium is substantiated, the differences tabulated must be considered significant. Unpublished data of K.A.C. Elliott favor the validity of the corrections made, but do not completely delineate possible changes in volumes of extra- and intracellular spaces which would affect the interpretation of these differences. These findings, in conjunction with previous findings of defects in acetylcholine binding and in glutamic acid metabolism (Project Serial #15 (C)), indicate an extensive and basic metabolic defect in epileptogenic brain tissue. In vitro additions of glutamine or asparagine or of ATP reverse



the defects in electrolyte metabolism, in a manner analogous to their reversal of defects in acetylcholine or glutamic acid metabolism. It is of some significance that these defects in electrolyte metabolism cannot be reproduced in cortica slices of cats in which seizures are induced with methionine sulfoximine and while a similar picture develops when normal cat cortex slices are incubated with 10% (instead of 95%) oxygen, no reversal with asparagine, glutamine or ATP is obtained. Thus different mechanisms clearly seem to be involved in the human epileptogenic cortex, exhibiting a unique defect in its ability to maintain tissue potassium concentrations. Since it is well established neurophysiologically that nerve conduction and transmission involve changes in intracellular potassium, these findings may have a more direct bearing on the actual neuronal firing in seizures. And there is evidence for an importance of potassium both in acetylcholine synthesis and in glutamic acid intracellular levels which may more closely inter-relate the components of the biochemical lesion in human epileptogenic cortex.

The findings of defects in acetylcholine binding (previously published), in glutamic acid metabolism and in electrolyte metabolism are all referrable to energy metabolism, since normal metabolism in each case depends upon supplies of energy as high-energy phosphate from adenosine-triphosphate (ATP) or creatine-phosphate. The fact that ATP, added <u>in vitro</u>, in each case reverses the defects in metabolism of epileptogenic slices is in favor of the concept that there may be a relative deficit in energy production or utilization by such slices as a fourth and perhaps basic component of the biochemical lesion. This is the first clear demonstration of an effect of ATP on incubated nervous tissue slices and has been shown not to be due to inorganic phosphate released or to other derivatives of ATP. Previous preliminary experiments suggest that ATP and creatine-phosphate are low in such slices and that added ATP may build up creatine-phosphate reserves.

(d) <u>Significance</u> of this project is self-evident since it brings into these studies on epileptogenic cortex two factors, electrolytes and energy supplies, which are accepted as essential to neuronal activity and function, providing much evidence for the mechanisms by which seizures can occur. If these findings can be clarified and extended, many of the missing links in the chain of circumstances underlining the seizure and concerned with neuronal activity in general can be set in place. This will represent a contribution not only to the problem of seizures but to neurophysiological mechanisms in general.

(e) <u>Proposed</u> course of this project falls into two main categories: (1) continuation of electrolyte studies particularly as concerns the problem of extra- and intracellular spaces and the exchange of sodium and potassium and (2) studies of energy metabolism in tissue slices by methods outlined above in order

to obtain some concept of the possible location of the defect in these systems. This is a difficult problem because of the many interlocking cycles of metabolism all of which are dynamically active. As a result considerable basic study will be required to develop methods which will be adequate for the purpose. Some of these will require detailed radioisotope studies with carbon-14 labelled compounds, which in themselves are methodologically very difficult

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-18 (C)
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY '55	$7,000	1	2	3	0.2	0.2	0.4	*
FY '56	$8,000	1	2	3	0.2	0.2	0.4	

* Patient material is derived from patients admitted for other NINDB projects.

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) ITEM 1

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15 NINDB-18 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Tower, D. B. "The Neurochemistry of Seizures" in Current Research in Neurochemistry and Allied Fields, edited by S. R. Korey and J. I. Nurnberger; New York, Paul B. Hoeber, 1955. In Press.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954.

None

Analysis of NIH Program Activities

Project Description Sheet

1. N.I.N.D.B. — INSTITUTE
2. Medical Neurology — LABORATORY OR BRANCH
3. Clinical Neurochemistry — SECTION
4. _____ — LOCATION
5. NINDB-19(C) — SERIAL NO.

6. Pentosuria in Neuromuscular Disease
PROJECT TITLE

7. Dr. Donald B. Tower
PRINCIPAL INVESTIGATOR

8. Dr. G. Milton Shy, Mr. Edmund Peters, Mr. Milton Pogorelskin
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(a) Objectives of this project are to assess the importance, if any, of pentosuria in patients with primary muscle disease and to identify the quantity and type of pentoses being excreted.

(b) Methodology: 24-hour urine samples are collected from NINDB ward patients who have been on a fruit-free diet for at least 48 hours (to avoid the complication of alimentary pentosuria). Aliquots of these urine samples are analyzed quantitatively for total free pentose by the method of Roe and Rice, using p-bromaniline as reagent and reading the color developed photocolorimetrically. Identification of pentoses present is done in two ways. Aliquots of urine are partially de-ionized by running them through Amberlite exchange resin columns (successively IR-120 cationic resin and IR-4B anionic resin), 100 microlitre portions are spotted on Whatman #1 filter paper sheets and run as paper chromatograms in two dimensions, using phenol and butanol-acetic acid respectively as solvents. Carbohydrate spots are developed with aniline-phthalate reagent and concentrations of each spot estimated by the spot area method. Standard concentrations of pentoses are run in each case. An alternate method for pentose identification is by use of the method of Moore and Link in which the benzimidazole derivatives of the pentoses are made by condensation with o-phenylenediamine and the individual pentose derivatives separated by fractional precipitation as potassium or barium salts.

(c) Patient material is obtained from NINDB ward patients. Neuromuscular disease patients are admitted to Medical Neurology for other studies and urine specimens provided for this project. Other patients with no muscle disease serve as controls and ar derived from other NINDB ward patients with eye diseases, multiple sclerosis, seizures and the like.

(d) Major findings:

The quantitative method of Roe and Rice for free urinary pentoses has been found to be specific and fully quantitative. No interference from glucose, glucuronic acid, ribonucleic acids, ascorbic acid or other carbohydrates or carbohydrate-like compounds has been found. Glucose in massive quantities, as in diabetic glycosuria, does interfere, but this has not been a factor in the cases studied. 24-hour excretions of as little as 5 - 10 mg. of free pentose can be accurately determined by this method.

A total of 35 patients have been studied, using the quantitative method. In most cases 24-hour specimens were collected and analyzed for at least a 5-day period in order to observe daily variations and to allow for incomplete collections. Thus, 150 - 200 patient samples have been studied. Of the 35 patients, 20 were diagnosed clinically as having intrinsic or primary muscle disease and 15 had no known muscle disease. Most of the muscle disease patients fell in the category of muscular dystrophy with others classed as myasthenia gravis or myotonia. The 24-hour free pentose excretion in all cases ranged between 5 and 150 mg. In general the control group rarely ranged above 35 mg. in 24 hours. In the primary muscle disease group a good proportion ranged above 60 mg. in 24 hours, but there were a number in the control range. No attempt has yet been made to analyze these results in detail since more control subjects are required to cover factors of age and sex.

In previous reports on this subject from other investigators it was felt that, on the basis of qualitative test estimates, there was a significantly and abnormally high excretion of free pentose in urines of muscular dystrophy patients. Data from this project suggest that many such patients excrete higher amounts, possibly double or triple expected amounts, but this is not true for all such patients and the total quantity, which rarely exceeds 100 mg. in 24 hours, is of an order that makes it difficult to consider this significant for the disease per se. In contrast, creatinurea, which is also known to occur in these and other patients, is of the order of 500 - 1500 mg. per day or higher. No attempt has yet been made to correlate level of pentose excretion with duration or clinical status of the disease, although it is an impression that in a few instances severely involved patients may show no elevation of urinary pentose excretion.

Previously published reports of other investigators have identified the pentose excreted as d-ribose, but careful perusal of these papers shows little if any basis for this conclusion, and one recent report failed to find any pentose by paper chromatography in a small series of cases. 24-hour urines from some 15 patients have now been analyzed by paper chromatography. In every instance the following sugars were clearly identifiable: glucose, arabinose and ribose. In addition to the latter two pentoses, xylose was present in traces in a majority and a spot tentatively identified as desoxyribose was present in several. A few have also given a spot in a position corresponding to glucuronic acid. From a relative quantitative standpoint ribose appears to predominate in urines from dystrophic patients, whereas arabinose appears to predominate in samples from controls.

Patients already in the series are being restudied to augment these data and the quantitative estimates are being extended.

The chemical isolation and identification of the pentoses present as the benzimidazole derivatives has not proven very practical for the quantities involved. With standard samples it has been shown that arabinose and ribose derivatives fall in the potassium salt fraction and can be easily separated by their differences in solubility. No published reports have appeared on the preparation of the benzimidazole from ribose itself, although Dr. Nelson Richtmeyer (NIAMD) and others have prepared it from the calcium salt of ribose. A sample prepared from ribose itself has now been made which, when compared with Dr. Richtmeyer's sample, was found to be identical chemically. Isolation from urine, as collected, was grossly interfered with by other urinary constituents and has been deferred until large capacity ion-exchange columns and low-temperature evaporators can be set up to overcome the dual problems of interfering substances and low concentrations.

(e) Significance of this project is primarily to establish definitively whether or not there is an abnormal degree or type of pentosuria in patients with primary muscle disease. Clues to the possible causes or mechanisms underlying muscular dystrophy in particular are virtually non-existent. It is important, therefore, to reach a conclusion about pentosuria, particularly since the literature is now confused and incomplete on this point. If there is a significant abnormality here, it will be of great importance and warrant extension to studies of blood and muscle. On the other hand definite negative evidence will be of service in directing efforts elsewhere and clearing confusion in the literature. Since neuromuscular diseases are one of the principal programs of NINDB, this project is important as one phase of that sudy.

(f) Proposed course of study includes collection of further clinical material, especially control data in terms of age and sex of patients which may affect amounts or types of pentoses excreted, and completion of chromatographic analyses of identities and relative quantities of pentoses being excreted. The isolation of pentoses as the benzimidazole derivatives will be re-tried in order to confirm chromatographic data. Finally the effect of brief acid hydrolysis of aliquots of urine samples will be studied both in relation to quantitative levels of pentoses as well as types of pentoses and relative concentrations. All these data are to be correlated with clinical data and routine urinalysis data obtained on each specimen.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-19 (C)
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$6,500	2	3	5	0.1	1.0	1.1	*
FY 1956	$7,550	2	3	5	0.1	1.0	1.1	

* Patient material used is derived from patients admitted to other NINDB projects.

12. BUDGET ACTIVITY

RESEARCH /X/ ADMINISTRATION /__/

REVIEW and APPROVAL /__/ TECHNICAL ASSISTANCE /__/

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956; IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH).

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-19 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

Analysis of NIH Program Activities
Project Description Sheet

1. N.I.N.D.B. (INSTITUTE) 2. Medical Neurology (LABORATORY OR BRANCH)
3. Clinical Neurochemistry (SECTION) 4. (LOCATION (IF OTHER THAN BETHESDA)) 5. NINDB-20(C) (SERIAL NO.)

6. Electrophoretic Studies of Human Cerebrospinal Fluid in Demyelinizing Diseases.
PROJECT TITLE

7. Dr. Israeli Jaffe and Dr. Donald B. Tower
PRINCIPAL INVESTIGATOR(S)

8. Dr. Charles E. Wells, Dr. William C. Curtis and Mr. Edmund Peters
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(a) Objectives of this project are to study the abnormalities in the protein fractions of cerebrospinal fluids from patients with multiple sclerosis in order to determine the significance of such abnormalities both diagnostically and prognostically in the clinical course of the disease.

(b) Methodology: Cerebrospinal fluid samples from NINDB ward or outpatients are obtained at lumbar puncture or pneumoencephalography. Aliquots of these samples are examined for routine constituents, including total protein content. The bulk of the fluid samples is then run by one of two methods of electrophoresis.

All samples for electrophoresis are concentrated 20 to 50 times by dialysis in cellophane or Visking dialysis bags against 20% P.V.P. or Dextran (synthetic high molecular weight polymers developed as blood plasma substitutes) in Saline or veronal buffer. 10-20 ml. samples of fluid are dialyzed against 300-500 ml. of 20% P.V.P. for 20 to 24 hrs. until the sample volume is 0.5 ml. or less.

Samples for paper electrophoresis are applied to strips of Whatman #3 filter paper as a band of 25 to 100 microliters volume. The strips are placed on a lucite frame, suitably sealed with ends dipping into Veronal buffer pH 8.6, ionic strength 0.05, and run horizontally by the "Sandwich" technique as modified by Sehon from the original method of Grassman and Svensson. After equilibration a current of 40 milliamps. is applied across the strip for 8 hours, which produces an albumen migration of 4-5 inches from the point of sample application. Strips are dried at 80°C for 12 hrs. and stained appropriately. Protein is stained with 0.1%

brom phenol blue alcoholic solution, containing acetic acid and mercury bichloride. Lipid complexes associated with protein fractions are stained with alcoholic Sudan Black Solutions, and carbohydrate complexes stained with periodic acid and Feulgen's reagent. The stained strips are dried at room temperature and read densitometrically by a densitometer to obtain relative percentages of components present.

Samples for micro-interferometric electrophoresis must be dialyzed against Veronal buffer containing P.V.P. to a concentration of not less than 1 g./100 ml. of protein and a volume not less than 0.4 ml. This requires a concentration of the original protein content by 30-40 times and an initial sample volume of 15 ml. or more. The 0.4 ml. concentrated sample is then placed in the μ-channel of the Kern LK-30 instrument with Veronal buffer pH 8.6, ionic strength 0.1 in the electrode chambers and a current and voltage producing not more than 200 milliwatts is applied. Sufficient migration, as checked in the eyepiece, to give good fringe separation is usually obtained by 1 hr. Photographic records of the interference fringe pattern are made as appropriate, the number of fringes giving the protein concentration and the grouping of fringes identifying the fractions and their relative percentages.

(c) Patient material: No patients have as yet been specifically admitted to this project. Patient material so far has been obtained from other NINDB project patients. As studies progress suitable patients with multiple sclerosis will be selected for serial study of their fluid patterns to permit correlation with the clinical state and progress of the disease.

Simultaneous blood serum samples will be run.

(d) Major findings: Much of the work to date has been methodological since no clear cut information on cerebrospinal fluid analytical techniques is available in the literature. A standard, reproducible and relatively simple paper method has been devised. This method permits good concentration of cerebrospinal fluid samples and electrophoretic patterns equal to or superior to any published for blood serum. Detailed studies with blood serum have demonstrated conclusively that serum diluted to the protein concentration of spinal fluid (1:200 dilution) can be reconcentrated without alteration of either protein fraction patterns or lipid fraction patterns. However, attempts to demonstrate any lipid staining material in association with spinal fluid protein fractions have all failed. Attempts by workers elsewhere have also failed. Ultra centrifuge studies by the Goffman technique have so far also failed to demonstrate lipid fractions, but the technical problems involved in this method have not all been overcome.

So far about 40 patients have been studied, some with multiple samples and with serum samples as well. 25 of these patients were diagnosed clinically as multiple sclerosis by NINDB neurologists. Although correlations of diagnosis and protein fraction pattern have not yet been made, about 12 or 50% of these samples show significant and definite elevation of the γ-globulin fraction. This elevation is an established fact from the immunochemical studies of Kabat, paper electrophoresis studies of several investigators and the chemical determinations of Roboz et al. None of these studies have assessed the diagnostic significance of this finding in multiple sclerosis and none of them have attempted to correlate the abnormality with clinical status and progress of this disease in the manner being undertaken here.

(e) Significance of this project is self-evident, since it represents a detailed study into an established chemical abnormality in a disease, multiple sclerosis, which is a major problem not only from a public health standpoint but from a diagnostic, prognostic and therapeutic standpoint. Nothing is known about its course or the mechanisms underlying its cause. With this first clue of biochemical abnormality a step in the direction of covering these many problems can be made by such a detailed and long-term approach.

(f) Proposed course of the project is to continue and extend studies already in progress. Specifically, it is intended to survey an equal number of patients more than already studied in order to have a sampling large enough to assess the diagnostic significance of the γ-globulin rise. In addition from this total group of patients serial studies will be continued to assess the correlation of the γ-globulin rise with exacerbations and remissions of the clinical disease with the view to establishing whether γ-globulin remains elevated or rises and falls and if so in what relation to the clinical status. Further attempts will be made to demonstrate lipid complexes using a modified lipid stain recently suggested by Dryer, and to study carbohydrate complexes, recently implicated in serum globulin abnormalities. Studies of related components such as hexosamine and presence of transaminases will also be considered and explored. More extensive studies with the micro-interferometric apparatus will be carried out now that the basic methods and patient material have been organized. Finally correlation of the two methods and the chemical method for γ-globulin will be made to assess their relative values in further studies.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-20(C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$6,000	3	2	5	0.5	0.2	0.7	*
FY 1956	$6,900	3	2	5	0.5	0.2	0.7	

* Patient material used is derived from patients admitted to other NINDB projects

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

National Heart Institute - Dr. Jaffe

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH).

None

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-20 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954.

None

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Clinical Research — LABORATORY OR BRANCH

3. Neurochemistry — SECTION
4. _____ — LOCATION (OTHER THAN BETHESDA)
5. NINDB-21 (C) — SERIAL NO.

6. Comparative Biochemistry of Smooth Muscle and Striated Muscle Actomyosin — PROJECT TITLE

7. Beni Horvath, M.D. — PRINCIPAL INVESTIGATOR(S)

8. None — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

OBJECTIVES: To characterize the uterine actomyosin in physico-chemical terms, preliminary to a study of actomyosin synthesis in the uterine muscle.

METHODS EMPLOYED: Myosin and actin will be prepared from rabbit uterine muscle and striated muscle. Yield will be compared at different stages of development of the uterus. The myosin and actin so obtained will be characterized by viscosity, electrophoretic mobility, sedimentation constant etc. as well as by its reaction with ATP.

MAJOR FINDINGS: For the purpose of comparison between the two kinds of muscle an extraction procedure had to be established and standardized giving maximal yield for both muscles. For the uterine muscle Caspo devised a method consisting of homogenization of the frozen muscle in an alkaline salt solution in the presence of ATP. It was verified now, that the same method gives as good yields on striated rabbit muscle as was obtained by H.H. Weber or by K. Bailey starting with fresh muscle. This method gives actomyosin. Actin and myosin may be isolated by the method of A. G. Szent-Gyorgyi's potassium iodide method.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: It is felt that studies of formation of myosin and actin may have a relationship to location of disease in muscular dystrophy. Quantitative extraction procedures are also essential for the study of proteins in Neuromuscular Disease.

PROPOSED COURSE OF PROJECT: Whereas the above method gives good yields for myosin, the actin yields may be improved, it is felt. As the ovarian hormones have a marked effect on the development of the uterus, the effect of these hormones will be studied on the time course of the protein synthesis in the uterine muscle, using the quantity of myosin and actin as a indicator.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-21 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$6,000	1	1	2	0.4	0.1	0.5	0
FY 1956	$6,900	1	1	2	0.4	0.1	0.5	0

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH).

None

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-21 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954.

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Clinical Research
LABORATORY OR BRANCH

3. Neurochemistry
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-22 (C)
SERIAL NO.

6. Alterations of Actomyosin Tensile Strength and Muscle Proteins in Neuromuscular Disease
PROJECT TITLE

7. Beni Horvath
PRINCIPAL INVESTIGATOR(S)

8. G. Milton Shy
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: To determine alterations in tensile strength of Actomyosin threads from biopsy material of patients with nauromuscular disease. To estimate the quantity of Actomyosin in diseased muscles and to characterize in physicochemical terms the proteins of diseased muscles as compared to normals.

Methods: Muscle fibers obtained from patients afflicted with Neuromuscular diseases were collected and preserved in glycerol at low temperature suitable for future analysis. The length tension relationship was studied with an isometric tension apparatus specially built, by applying quick stretches and releases, in the presence of adenosine triphosphate. (ATP) Other samples also obtained on biopsy were collected and stored in the frozen state. These samples were extracted with salt solutions. Nitrogen determinations and viscosimetric measurements were undertaken on these extracts. Threads were prepared from Actomyosin and the speed of contraction noted in the presence of adenosine triphosphate.

Patient material: Muscle sample obtained from patients afflicted with neuromuscular diseases, under nerve block anesthesia

Major findings: Preliminary studies on glycerinated fibers of the Rabbit psoas yielded length tension diagrams similar to the ones obtained in other laboratories by different investigators. For the purpose of comparison it was necessary to establish the

Magnesium concentration and ATP concentration, optimal for tension development.
Quantitative extraction of actomyosin from small muscle samples has previously been solved for heart and uterine muscle. It never was a problem as far as striated muscle goes. It was found, that a strong, alkaline salt solution supplemented with ATP gives the highest yields. The muscle has to be homogenized and the extraction continued for 24 hours.
Significance: The project is part of an integrated effort involving many disciplines to learn about the nature of such diseases as muscular dystrophy, myasthenia gravis and myotonia.
Proposed course: The tension measurements so far could be characterized as baseline studies. They have to be repeated on a fairly large number of fibers from different diseases. It seems to be desirable to extend the method to include continuous length tension diagrams. The effect of added substances or treatment to the patient will be studied on the tension developed. Specifically, the investigation of the relaxing substance (ATP-CP transphosphorylase) in myotonia seems to be of interest.
Characterization of the diseased muscle proteins is proposed by means of the ultracentrifuge, electrophoresis and conductivity measurements.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-22 (C)
SERIAL NO.

11. _____
BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$7,000	1	1	2	0.6	0.7	1.3	
FY 1956	$8,000	1	1	2	0.6	0.7	1.3	

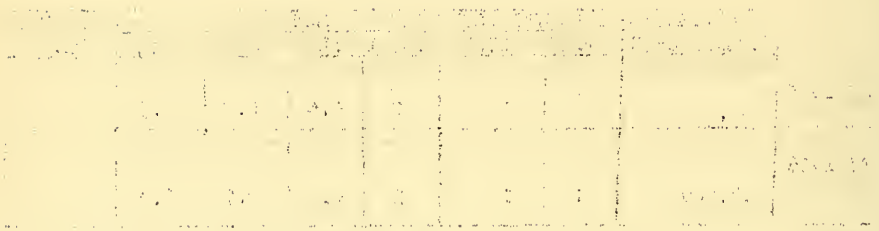
12. BUDGET ACTICITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) .

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)



R.P.C.
December 1954 Analysis of NIH Program Activities

Honors, Awards and Publications Sheet

15. NINDB-22 (C)
SERIAL NO.

None

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. N.I.N.D.B. (INSTITUTE) 2. Medical Neurology (LABORATORY OR BRANCH)

3. Clinical Neurochemistry (SECTION) 4. _____ (LOCATION) 5. NINDB-23(C) (SERIAL NO.)

6. The Nature and Characterization of the Pyrogen and Similar Molecules
PROJECT TITLE

7. Dr. William C. Curtis
PRINCIPAL INVESTIGATOR

8. Dr. Donald B. Tower; Dr. William Windle
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(a) Objectives of this project are to study the physical and chemical properties of pyrogen molecules and related molecules such as oxyproteic acids with a view to characterizing them and determining their nature. The recent demonstration of anatomical and physiological regeneration of central nervous tissue coincident with pyrogen therapy focusses attention on the importance of these agents in nerve tissue metabolism and repair. Since the chemical and physical nature of such compounds is poorly understood, their mechanism of action and factors concerned with their glial inhibitory property remain obscure.

(b) Methodology: Starting with the pyrogen, Piromen, preliminary purification by ion exchange, column chromatography, foam fractionation and absorption will be carried out. The initial characterization will be by classical physico-chemical means, including electrophoresis, diffusion, sedimentation velocity and equilibrium, selective adsorption, and solubility studies. Further studies will depend upon the results of these steps.

(c) Patient Material will not be used for this project initially.

(d) Major Findings are none to date. This project has been set up only two months, which have been devoted to collecting and designing equipment necessary for the methods outlined above.

(e) Significance of this project has been indicated under objectives. This is a more basic study which is designed to throw light on mechanisms underlying the action of these agents in experimental therapy. They also relate to the fundamental problem of fever mechanisms which are of great importance as causative agents of many destructive processes in central nervous tissue.

(f) Proposed course of the project is to undertake the studies outlined above under methodology.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-23 (C)
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$6,000	2	3	5	0.6	0.2	0.8	0
FY 1956	$6,900	2	3	5	0.6	0.2	0.8	0

12. BUDGET ACTIVITY

RESEARCH [X] ADMINISTRATION [ ]

REVIEW and APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

Laboratory of Neuroanatomical Sciences, NINDB - Dr. Windle
(Serial No. NINDB-5 (L))

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH).

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-23 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness (INSTITUTE) 2. Surgical Neurology (BRANCH)

3. Neurosurgical Service (SECTION) 4. _____ (LOCATION) 5. NINDB-24 (C) (SERIAL NO.)

6. Investigation of the Second Sensory Areas in Man
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. J. M. Van Buren, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To outline the extent and nature of these sensory representations in man and if possible discover their functional significance.

Methods Employed: 1. Electrical stimulation of these areas under local anesthesia during operative exposure.
2. Recording of these results.
3. Electrographic recording during these stimulations.

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Male	14	45
	Adult Female	6	46
	Children Male	0	
	Children Female	0	
Outpatient:	Number of patients:	0	
	Number of visits:	0	

Major Findings: We have evoked positive responses relative to the second sensory areas in 18 patients. These responses indicate that there is a typical representation in this area.

Significance to Neurological Research: This is a relatively unknown area of brain function. Knowledge of its function is important to our understanding of the sensory mechanisms of the brain and is essential to our knowledge of temporal lobe epilepsy since epileptogenic lesions often activate this area and their expression is not clearly understood.

R.P.C. - 1 (a)
Dec. 1954

PROJECT DESCRIPTION (Continued)

Proposed course of the Project: We must continue stimulations of these areas in man and reinforce the knowledge gained from these stimulations by evoked potential studies in the operating room. This work will be substantiated and reinforced by observations on the brains of higher primates as well.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-24 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$4,100	2	--	2	0.6	--	0.6	
FY 1956	$4,200	2	--	2	0.6	--	0.6	

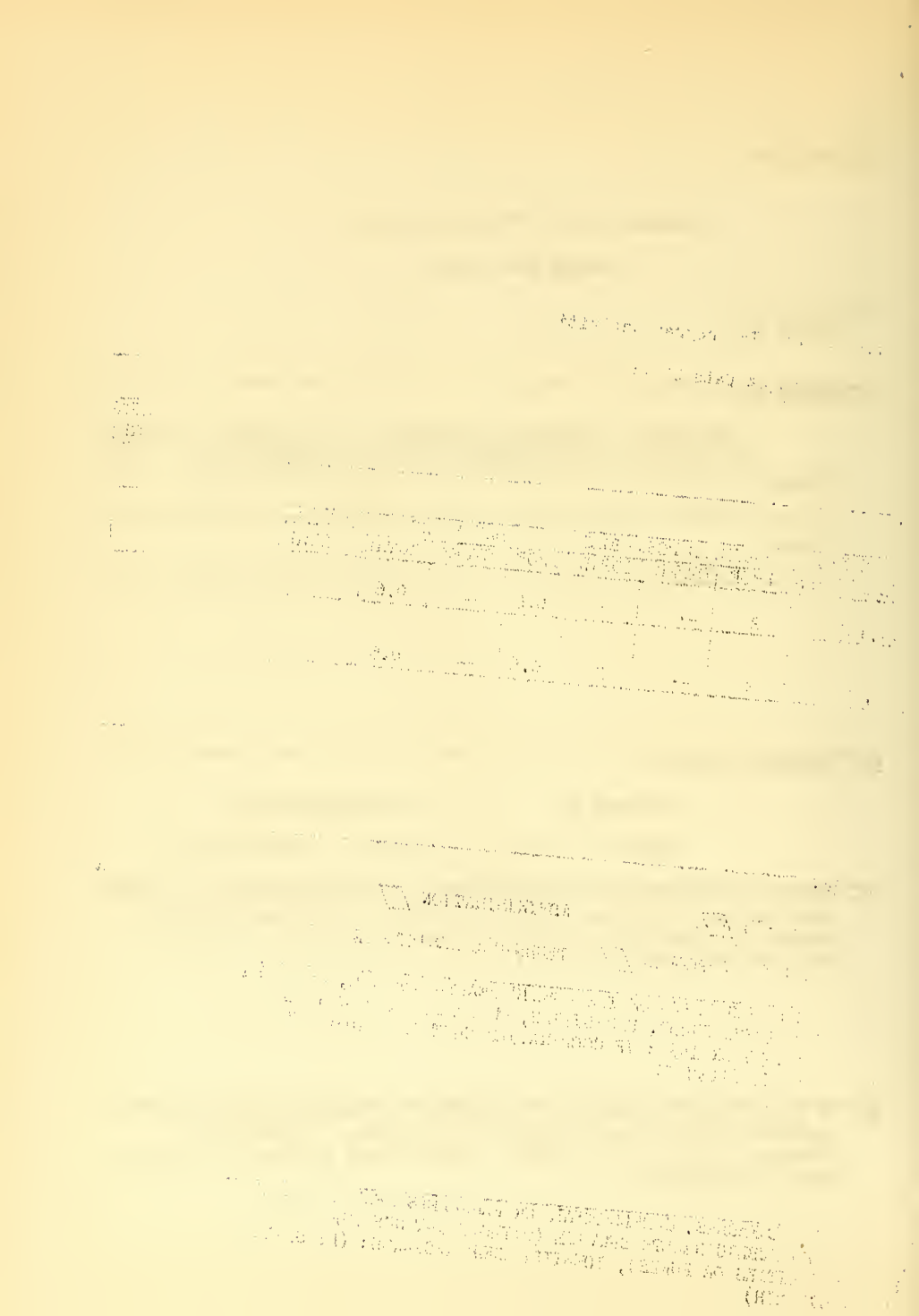
12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)



R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-24 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954.

R.P.C. 1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Surgical Neurology — BRANCH
3. Neurosurgical Service, Experimental Neurosurgery — SECTION
4. _____ — LOCATION
5. NINDB-25 (C) — SERIAL NO.
6. A Study of Involuntary Movements — PROJECT TITLE
7. Maitland Baldwin, M. D. — PRINCIPAL INVESTIGATOR
8. Bruce Ralston, M. D. and J. M. Van Buren, M. D. — OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: To study the mechanisms of involuntary movements in man.

Methods Employed:
1. Clinical neurological examination
2. Photographic analysis
3. Interruption of extrapyramidal pathways in man and the higher primates.

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Male	4	49
	Adult Female	1	57
	Children Female	2	24
	Children Male	0	
Outpatient:	Number of patients:	1	
	Number of visits:	3	

Major Findings: We have developed a technique for analyzing involuntary movements. This involves the use of stroboscopic photography and it is most useful in determining the rate range and nature of these movements. In one case we have begun an electromyographic analysis as well. This provides some information concerning individual muscle action in these complicated movement patterns. In monkeys we have created lesions in the region of the caudate and putamen and in one animal have developed some involuntary movements including tremor at rest.

Significance to Neurological Research: The origin and precise physiological cause of involuntary movements are unknown. The clinical neurologist requires this information for without it he can do nothing

PROJECT DESCRIPTION (continued)

for this tragic group of patients who are otherwise lost to useful society. Further knowledge of these movements is actually knowledge of the extrapyramidal system and we need this knowledge if we are to understand the structural basis of normal voluntary movement.

Proposed Course of Project: We will continue our clinical observations with present techniques and devise new methods of observation. In the operating room we hope to undertake recognized surgical procedures for the relief of these incapacitating conditions and study the effects of these procedures. In the primate laboratory we hope to study more of the precise anatomy of the extrapyramidal system and create lesions within so as to study the effect of defects in this primitive motor pathway.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-25 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$6,200	3	--	3	0.9	--	0.9	
FY 1956	$6,300	3	--	3	0.9	--	0.9	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-25 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness (INSTITUTE) 2. Surgical Neurology (BRANCH)

3. Neurosurgical Service (SECTION) 4. _____ (LOCATION) 5. NINDP-26 (C) (SERIAL NO.)

6. An Investigation of Speech Function Localized in the Temporal Areas of Man
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. Laurence Frost, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To outline the extent of cortical speech representation in man and to understand the relative significance of the areas outlined in speech functions.

Methods Employed: 1. Electrical stimulation of the temporal and parietal cortex in patients during operations under local anesthesia.
2. Clinical examination of speech function before and after such operations.

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Male	14	45
	Adult Female	6	46
	Children Male	0	0
	Children Female	0	0

Outpatient:	Number of patients:	0
	Number of visits:	0

Major Findings: We have outlined an area concerned with motor speech, and two areas concerned with the meaning of speech. We can arrest speech but we cannot evoke it by direct stimulation. This implies that there are complicated subcortical connections related to speech which we do not activate by stimulation.

Significance to Neurological Research: Speech is among the most complicated functions of the human brain. We know little of its intrinsic mechanisms. Some knowledge of these functions provides great assistance to the neurologist in diagnosis of brain disease

PROJECT DESCRIPTION (continued)

and in the rehabilitation of those with brain lesions. This project relates to the one on vestibular and auditory function and also to the psychological study of speech. In combination these projects should provide information of value to the neurologist, psychologist and psychiatrist.

Proposed Course of Project: We will continue along present lines and add more precise methods of testing speech in the operating room as well as methods designed to outline the cortical representations of hearing and vestibular function.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-26 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$4,100	2	--	2	0.6	--	0.6	
FY 1956	$4,200	2	--	2	0.6	--	0.6	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-26 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954.

R.P.C. 1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Surgical Neurology — BRANCH
3. Neurosurgical Service, Experimental Neurosurgery — SECTION
4. _____ — LOCATION
5. NINDB-27 (C) — SERIAL NO.
6. Pain Pathways in Man and the Higher Primates — PROJECT TITLE
7. Maitland Baldwin, M. D. — PRINCIPAL INVESTIGATOR
8. Bruce Ralston, M. D. — OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: The study of pain mechanisms in man with special reference to those surgical techniques which may be utilized in relief of intractable pain.

Methods Employed:
1. Clinical examination
2. Nerve blocks
3. Anesthetic and analgesic agents
4. Surgical interruption of pain pathways

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Males	3	37
	Adult Females	1	101
	Children Male	0	
	Children Female	0	
Outpatient:	Number of patients:	5	
	Number of visits:	9	

Major Findings: We have investigated the pathways subserved by the fifth cranial nerve at operation when the trigeminal ganglion is available for stimulation and the intracranial vessels are also available for this electrical stimulation. This has provided information concerning intracranial pain pathways.

Also we have studied the effect of herpes zoster virus in the fifth nerve pathways in one patient and tested various blocking agents in an attempt to relieve this intractable pain.

In one patient, who had metastatic carcinoma and intractable pain, we have studied the effects of frontal leucotomy on this pain; and in another who had pain of central origin we have tested the efficacy of local blocking agents and centrally acting drugs.

PROJECT DESCRIPTION (continued)

Significance to Neurological Research: The clinical neurologist must solve the problems of those with intractable pain. Any clinician who treats advanced cancer knows the great need for more effective pain relief is urgent.

A knowledge of pain pathways which is more complete will advance clinical methods as well as physiological discovery.

Proposed Course of Project: We would like to study the effects of interruption of the pain pathways in man and the primates and thus permit the development of new techniques for the resolution of what is now called intractable pain. These interruptions may be either pharmacological or surgical.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-27 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$8,200	2	2	4	0.6	0.6	1.2	
FY 1956	$8,300	2	2	4	0.6	0.6	1.2	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-27 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954.

R.P.C. 1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Surgical Neurology — BRANCH
3. Neurosurgical Service, Experimental Neurosurgery — SECTION
4. _____ — LOCATION
5. NINDB-28 (C) — SERIAL NO.
6. An Investigation of the Autonomic Phenomena which Follow Stimulation of the Temporal Areas in Man and the Higher Primates — PROJECT TITLE
7. Maitland Baldwin, M. D. — PRINCIPAL INVESTIGATOR
8. J. M. Van Buren, M. D., Laurence Frost, M. D., Charles Wood, M. S., Shirley Lewis, R. N. — OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: To further understanding of the central representations of autonomic function.

Methods Employed: 1. Electrical stimulation at operation.
2. Electrographic and electronic recording during this stimulation.

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Males	13	45
	Adult Females	5	46
	Children Male	0	
	Children Female	0	

Major Findings: In patients at operation under local anesthesia we have observed changes in blood pressure, pulse, respiration and gastric motility following stimulation of the insula; following stimulation of the amygdaloid nucleus we have observed changes in respiration and in pulse rate.

In chimpanzees and in monkeys we have observed similar changes.

Significance to Neurological Research: Central representation of autonomic function is not clearly understood. These central representations which we have outlined are important in the understanding of the structural basis of emotions and in the understanding of the central control of the cardiovascular and respiratory systems.

PROJECT DESCRIPTION (continued)

Proposed Course of Project: We must outline the exact nature of these autonomic changes which follow central stimulation in man. We have entered mechanisms which are important in neurology as well as in the understanding of changes in the cardiovascular and respiratory systems.

We will continue electrical stimulation of these areas in man and the higher primates and attempt to make our recording of the results more exact by additional techniques, both in man and the primates.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-28 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$10,300	3	2	5	0.9	0.6	1.5	
FY 1956	$10,500	3	2	5	0.9	0.6	1.5	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-28 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954.

R.P.C. 1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Surgical Neurology — BRANCH
3. Neurosurgical Service; Experimental Neurosurgery — SECTION
4. _____ — LOCATION
5. NINDB-29 (C) — SERIAL NO.
6. Mechanisms of Memory — PROJECT TITLE
7. Maitland Baldwin, M. D. — PRINCIPAL INVESTIGATOR
8. Laurence Frost, M. D. — OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: To further our understanding of those functional representations within the temporal lobe of man and the higher primates which may subserve the mechanisms of memory.

Methods Employed: 1. Electrical stimulation of the human temporal lobe during operative exposure under local anesthesia.
2. Ablation of the temporal areas in higher primates.

Patient Material:

			Average Stay - days
Admissions:	Adult Male	12	45
	Adult Female	5	46
	Children Male	0	0
	Children Female	0	0
Outpatient:	Number of Patients:	0	
	Number of Visits:	0	

Major Findings: In six patients we have elicited responses related to the memory mechanisms. These might indicate that there are neuronal patterns in the temporal area which subserve the memory mechanisms.

We have ablated the temporal areas on both sides in one chimpanzee. She is infantile and immature in behaviour but she has not lost conditioning patterns essential to feeding, grooming or cage play. We have ablated these areas in eight monkeys and six cats. The monkeys become infantile and lose adaptability in dealing with cage mates.

Significance to Neurological Research: This project and those allied with it in the Section of Clinical Psychology, serve to provide some data on the physiological basis and perhaps on the structural basis for memory. A major effort is being directed towards the establishment of data which will provide an understanding of some of the structural bases for mental functions and therefore for mind.

PROJECT DESCRIPTION (continued)

Proposed Course of Project: We plan a continuation of our present study of those neuronal patterns in the temporal lobe which subserve memory. The combination of information derived from direct electrical stimulation of the temporal lobe in man with information derived from studies of humans and higher primates in which the temporal areas have been ablated should provide useful and perhaps significant information concerning the structural basis for mind.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-29 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$4,100	2	--	2	0.6	--	0.6	
FY 1956	$4,200	2	--	2	0.6	--	0.6	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-29 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Psychological Changes after Temporal Lobectomy. Maitland Baldwin, M.D. Read before the International Congress of The American College of Surgeons, Lima, Peru.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954.

R.P.C. 1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Surgical Neurology — BRANCH
3. Neurosurgical Service / Experimental Neurosurgery — SECTION
4. _____ — LOCATION
5. NINDB-30,(C) — SERIAL NO.

6. Epileptogenic Mechanisms in the Brain of Man
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. C. Ajmone-Marsan, M.D., J.M. Van Buren, M.D., Bruce Ralston, M.D.
D.B. Tower, M.D., E.C. Alvord, M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To study causal mechanisms of epileptic seizures in man:

a. To study the characteristics of epileptogenic areas in the brain of man.
b. To study the characteristics of the lesions which predispose to epileptogenic changes in the brain of man.
c. To study the clinical expression of these epileptogenic areas in man.
d. To study the electrographic characteristics of epileptogenic activity in the brain of man.
e. To study the approved methods of surgical therapy for these lesions and develop new therapeutic methods.
f. To study brain function as it is exposed in the extravagant experiments devised by these lesions.

Methods Employed:

a. Clinical neurological examination
b. Special radiographic examination
c. Electrographic examination
d. Electrocortigraphic examination
e. Electrical stimulation of the lesion exposed at operation
f. Selective isolation of the lesion at operation
g. Cinematographic and sound recording
h. Histological and chemical examination

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Male	46	32
	Adult Female	33	46
	Child Male	15	30
	Child Female	14	62

Outpatient:	Number of patients:	97
	Number of visits:	118

PROJECT DESCRIPTION (continued)

Major Findings: We have observed and recorded new characteristics in the clinical pattern of cerebral seizures arising in one or the other temporal lobe in man. These are new in that they have not been previously described. Knowledge of them assists in future diagnosis and treatment. We have studied the local and distant effects of epileptogenic activity in the amygdaloid nucleus in man and the higher primates and we have isolated an epileptogenic area in the cortex of man and recorded activity from it during operation. This isolation was effected by selective undercutting.

We have studied automatic behaviour following temporal lobe seizures in man and now recognize that it takes several different forms. We have also evoked this behaviour in primates through artificial epileptic discharge in temporal lobe.

We have analyzed the motor phenomena of temporal lobe seizures in man and in the primates.

In cooperation with the Branch of Electroencephalography we have analyzed the seizure patterns in the laboratory and in the operating room.

In cooperation with the Sections of Neurochemistry and Neuropathology we have begun the analysis of the chemical and pathological characteristics of those epileptogenic lesions which we see at operation.

In cooperation with the Dept. of Social Work we have begun and are continuing a study of the social factors which influence the family, community or institution which contain individuals who are epileptic.

In cooperation with the section of Clinical Psychology we are studying and have studied personality characteristics in these cases.

Significance to Neurological Research: There is no satisfactory and complete treatment for epilepsy at present. Medication improves some cases, surgery offers hope of a cure to some and helps others, but neither of these methods is sufficiently advanced to solve the growing and tragic problem of epilepsy in this country today. There are over one and one half million epileptics in the United States at present according to hospital statistics and the actual number is probably much larger. These people require help urgently and if help is not effective they become social and economic liabilities. Only carefully planned neurological research can provide the basis for effective help.

Epilepsy may occur anywhere in the brain and wherever it occurs it mirrors the function of that part of the brain which it affects. Therefore the neurologist can study the functions of the brain if he studies the epileptic carefully and supplements his clinical observations with scientific experiments.

Proposed Course of Project: We will continue the clinical studies. With new methods of electrographic recording and stimulation we must expand our area of observation in the human operating room. In the primate laboratory we plan to create epileptogenic lesions and study their course and effects. Also we hope to study the spread of epileptic discharge in the human and in the primate and we must expand our social studies of these patients. In therapy we hope to improve our surgical technique and devise new ones; and we hope to test new medications and assist in the evaluation of the new experimental chemical treatment.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-30(C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$14,500	6	1	7	1.9	0.3	2.2	
FY 1956	$14,700	6	1	7	1.9	0.3	2.2	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-30 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954.

R.P.C. 1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness (INSTITUTE) 2. Surgical Neurology (BRANCH)

3. Neurosurgical Service Experimental Neurosurgery (SECTION) 4. _____ (LOCATION) 5. NINDB-31 (C) (SERIAL NO.)

6. A Study of Functional Representation in the Amygdala of Man and the Higher Primates
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. L. L. Frost, M. D., C. D. Wood, M. S., Shirley Lewis, R. N.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To further understanding of the functions and functional connections of this important nucleus in man and the higher primates.

Methods Employed: 1. The electrical stimulation of the amygdaloid nucleus in patients under local anesthesia during operative exposure of the temporal regions.

2. The electrical stimulation of the amygdaloid nucleus in higher primates during operative exposure of the temporal regions and as chronic preparations after implantation of deep electrodes.

3. Electrographic recording from the temporal, parietal, frontal and deep temporal regions during these electrical stimulations.

Patient Material:

		No.	Average Stay - Days
Admissions:	Adult Males	13	45
	Adult Females	5	46
	Child Male	0	
	Child Female	0	
Outpatient:	Number of patients	0	
	Number of visits	0	

Major Findings: We have developed a technique and an instrument for stimulation of the amygdala in patients during operation. With this technique we have evoked responses from this nucleus in 18 patients. These responses are motor and autonomic. The motor responses are movements of face and jaws; the autonomic are changes in respiration and pulse rate.

In monkeys we explored this nucleus with the Horsley-Clarke instrument and stimulated it in precise areas. We have also implanted electrodes in monkeys and studied them during stimulation of the nucleus

PROJECT DESCRIPTION (continued)

as chronic preparations. Furthermore we have stimulated this nucleus on both sides in one chimpanzee. In all these animals we have elicited movements of the face and jaw and autonomic changes following these deep stimulations. These stimulations are followed by a diffuse alteration in the cortical electrical activity as well. This is most marked in the parietal regions and we have observed it in both the patients and the animals.

Significance to Neurological Research: The amygdaloid nucleus is an important and central mechanism within the temporal lobe. It has functions related to face and jaw movement, autonomic function, and behaviour as well as the mechanisms of consciousness. We must understand it and its connections if we would understand temporal lobe epilepsy.

Proposed Course of Project: We are continuing the stimulation of this nucleus in man and in the primates. We are conducting a thorough study of its anatomical connections in the primates and we are studying the problems of behaviour in man and the primates as well as the electrophysiological problems related to the stimulations in both man and the primates. Future studies of this kind should provide important information concerning the mechanisms of temporal lobe epilepsy and certain aspects of behaviour and the mechanisms of consciousness.

R.P.C. -2
December 1954

NINDB-31 (C)
SERIAL NO.

Analysis of NIH Program Activities

Budget Data Sheet

10. _____
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$8,200	2	2	4	0.6	0.6	1.2	
FY 1956	$8,300	2	2	4	0.6	0.6	1.2	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-31 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Investigation of the Primate Amygdala: Movements of the Face and Jaws. Baldwin, M., Frost, L. and Wood, C. Neurology, Aug. 1954.

Investigation of the Primate Amygdala: Ablation and After Discharge. ibid: in press.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954.

R.P.C. 1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Surgical Neurology — BRANCH
3. Neurosurgical Service — SECTION
4. _____ — LOCATION
5. NINDB-32 (C) — SERIAL NO.
6. Anatomy of the visual pathways — PROJECT TITLE
7. J. M. Van Buren, M. D. — PRINCIPAL INVESTIGATOR
8. _____ — OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: Re-examination of the anatomy of the visual pathway in man and monkey.

Methods Employed: Human autopsy and monkey degeneration material--staining principally by Golgi technique.

Patient Material: Admission for terminal care of patients with lesions of the optic pathways. (Not over two at a time.)

Major Findings: A useful Golgi method for formalin-fixed autopsy material.

R.P.C. 2
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-32 (C)
SERIAL NO.

11. BUDGET DATA

	EST. EXPEND.	BUDGETED POSITIONS PROF.	OTHER	TOTAL	MAN YEARS PROF.	OTHER	TOTAL	PATIENT DAYS
FY 1955	$6,200	1	2	3	0.3	0.6	0.9	
FY 1956	$6,300	1	2	3	0.3	0.6	0.9	

12. BUDGET ACTIVITY:

RESEARCH [x] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE IDENTIFY SUCH PROJECT.

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-32 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Surgical Neurology
LABORATORY OR BRANCH

3. Experimental Neurosurgery
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA

5. NINDB-33 (C)
SERIAL NO.

6. Micro-electrode Studies of the Cerebral Cortex in Experimental Animals and Man.
PROJECT TITLE

7. Choh-Luh Li, M. D.
PRINCIPAL INVESTIGATOR(S)

8. None.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Project: Development of methods for recording electrode activity of single cells from the human cortex.

Objectives: To develop methods which can be adapted in the human operating room for the recording of electrical activity of single cortical cells, particularly in epileptic patients, with the purpose of studying the mechanism of epilepsy.

Methods Employed: Micro-electrodes made of glass capillary pipettes with an inside diameter of less than half a micron are used for recording electrical activity from single cells.

Major Findings: The major findings of this project during the past four months has been the development of a special apparatus which is capable of

manipulating the recording micro-electrodes without the interference of brain movements. This apparatus has been proven to be effective in experiments on monkeys and chimpanzees and is expected to be useful on human patients in the near future. During the same period, micro-electrode recording from the cortex of cats and monkeys has provided further information on the activity of cortical cells; for example, the action potential and membrane potential of single cortical cells in the somatosensory cortex of the cat have been determined and reports of this study have been submitted for publication. In addition, similar reports have been made on the study of evoked potentials from single cortical neurones. In the last month the recording device has also been completed for the recording of two neighboring cortical cells. The preliminary findings indicate that the cortical neurones do not discharge synchronously, whether recorded under normal conditions or during epileptic processes.

Significance to NINDB Research: In order to learn the function of the cortex, the behavior of the cortical unit is basically important and this research project is directly concerned with this problem.

Proposed course of project: During the next year our work is to be devoted to the study of epileptic discharges in terms of cortical cell activity. This study will be carried out on cortices of experimental animals, as well as human patients.

R.P.C. - 2
December 1954 Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-33 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$4,000	1	1	2	0.3	0.3	0.6	
FY 1956	$4,200	1	1	2	0.3	0.3	0.6	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1

Dr. Wade Marshall, Chief, Laboratory of Neurophysiology, NIMH, SER. NO._____
Dr. Carl Frank, Chief, Section on Spinal Cord, NINDB, Ser. No._____

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

R.P.C. - 3
December 1954 Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-33 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Awaiting Publication:

1. Membrane Potentials and Action Potentials of Cortical Neurones.
2. Laminar Analysis of Cortical Evoked Potentials.
3. Laminar Analysis of Unspecific Recruiting Responses.
4. Interaction of Specific Responses and Unspecific Responses.
5. Facilitation of Cortical Sensory Neurones Under the Influence of Unspecific Thalamic Nuclei.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Surgical Neurology — BRANCH
3. Clinical Neuropathology — SECTION
4. _____ — LOCATION
5. NINDB-34 (C) — SERIAL NO.

6. Relation of Supraspinal Structures to an Experimental Startle Reaction
PROJECT TITLE

7. Ellsworth C. Alvord, Jr., M. D.
PRINCIPAL INVESTIGATOR

8. David G. Whitlock, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To determine the neuroanatomical and physiological substrata of the startle reaction.

Methods Employed: Acute and chronic lesions of the central nervous system of cats have been made in various locations to determine the effects of such lesions upon the generalized muscular contractions which can be reflexly evoked by various suddenly applied stimuli in cats under chloralose anesthesia. Other experiments have been performed utilizing a stereotaxically oriented electrode to explore the C.N.S., both by recording evoked electrical potential from and by applying single electrical stimuli to localized regions of the C.N.S.

Major Findings: The spinal cord has been found to be not sufficient for the generalized reflex myoclonic reaction elicitable in cats under chloralose anesthesia. A weak response occurs in chronic decerebrate preparations, and a strong reaction occurs in chronic decorticate cats. Investigation of the "reticular formation", especially of the midbrain, reveals that both sides of the body project to this region, and that stimulation here produces a bilateral motor response in the lumbosacral ventral roots. With a dual beam cathode ray oscilloscope the latency of the responses in the midbrain and in the lumbar ventral roots were compared. The anatomical distribution of the reactions was determined histologically from serial sections of the C.N.S. The site of maximal projection to the midbrain reticular formation and the site of lowest threshold voltage for effective stimulation of the midbrain reticular formation were almost identical.

Significance to Neurological Research: Study of the startle reaction provides basic information concerning the organization of the nervous system, particularly with respect to its more diffusely organized functions, and is of importance in the understanding of reflex activity in general and perhaps of reflexly induced epileptic seizures in experimental animals and patients. Since chloralose is frequently used in neurophysiological experiments, further knowledge of its actions is also important.

9. PROJECT DESCRIPTION: (continued)

Proposed Course of Project: The above experiments are being critically reanalyzed and retested prior to submission for publication, following which further experiments are not planned.

R.P.C. 2
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-34 (C)
SERIAL NO.

11. BUDGET DATA

	EST. EXPEND.	BUDGETED POSITIONS PROF.	OTHER	TOTAL	MAN YEARS PROF.	OTHER	TOTAL	PATIENT DAYS
FY 1955	$1,095	1	--	1	0.2	--	0.2	
FY 1956	$1115	1	--	1	0.2	--	0.2	

12. BUDGET ACTIVITY:

RESEARCH [x] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.

Army Medical Service Graduate School, Walter Reed Army Medical Center, Dr. David G. Whitlock.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE IDENTIFY SUCH PROJECT.

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-34 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

1. "A comparison of generalized reflex myoclonic reactions elicitable in cats under chloralose anesthesia and under strychnine." Am. J. of Physiology, 6:253, 1954, Ellsworth C. Alvord, Jr. and Michael G. F. Fuortes.

2. "The role of the brainstem in generalized reflex myoclonic reactions in cats under chloralose anesthesia." Federation Proceedings, 13:2, 1954, Ellsworth C. Alvord, Jr., and David G. Whitlock.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C. 1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Surgical Neurology — BRANCH
3. Clinical Neuropathology — SECTION
4. _____ — LOCATION
5. NINDB-35 (C) — SERIAL NO.

6. Histopathologic investigation of granulomatous uveitis and other diseases of the eye
PROJECT TITLE

7. Ellsworth C. Alvord, Jr., M. D.
PRINCIPAL INVESTIGATOR

8. Ralph Ryan, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To determine the histopathologic alterations of the eye in various diseases in human patients and in experimental animals.

Methods Employed: Sections of the eye following paraffin or celloidin embedding will be stained appropriately for the detection of inflammation and organisms.

Patient Material: Patients are obtained through the Ophthalmology Branch, NINDB.

Major Findings: Eleven eyes have been obtained either at operation or at autopsy from patients with a variety of ophthalmologic disorders. Only a few have been examined histologically pending the development of sufficiently precise histopathologic techniques.

Significance to Neurological Research: The determination of precise morphologic abnormalities in eyes removed in operation is of great importance in the diagnosis and management of such patients.

Proposed Course of Project: With the acquisition and training of sufficiently skilled histopathologic technicians, the eyes will be sectioned and examined. It is hoped that more liberal autopsy permissions may permit removal of the eyes more often. Experiments in animals are also planned.

R.P.C. 2
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-35 (C)
SERIAL NO.

11. BUDGET DATA

	EST. EXPEND.	BUDGETED POSITIONS PROF.	OTHER	TOTAL	MAN YEARS PROF.	OTHER	TOTAL	PATIENT DAYS
FY 1955	$8,180	2	3	5	0.3	1.2	1.5	
FY 1956	$8,340	2	3	5	0.3	1.2	1.5	

12. BUDGET ACTIVITY:

RESEARCH [x] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.

Ophthalmology Branch, NINDB, Dr. Ralph Ryan (NINDB-44 (C))

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE IDENTIFY SUCH PROJECT.

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-35 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness (INSTITUTE) 2. Surgical Neurology (BRANCH)

3. Clinical Neuropathology (SECTION) 4. _____ (LOCATION) 5. NINDB-36 (C) (SERIAL NO.)

6. Pathogenesis of "allergic" encephalomyelitis
PROJECT TITLE

7. Ellsworth C. Alvord, Jr., M. D.
PRINCIPAL INVESTIGATOR

8. Norman Goldstein, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To determine the cause and the mechanism underlying the development of disseminated encephalomyelitis.

Methods Employed: Brain and various extracts of brain are prepared in a water and oil emulsion with killed acid-fast bacilli. Following subcutaneous inoculation into guinea pigs, the animals are examined for clinical evidence of weakness, incoordination, or other neurological disorder. The spinal cord and brain are examined histologically for presence of characteristic perivascular inflammation sometimes with demyelinization.

Major Findings: 210 guinea pigs have been sacrificed for neuropathologic survey for the presence or absence of the experimental disease. Unfortunately the shortage of adequately trained personnel has permitted examination of only 20 of these so far. As soon as possible the others will be studied histologically, and the lesions correlated with clinical observations and with the chemical fraction of the brain included in the vaccine to produce the disease.

Significance to Neurological Research: Study of the etiology and pathogenesis of "allergic" encephalomyelitis in experimental animals will yield information of importance to patients treated with vaccines containing brain material, as in anti-rabies inoculations, and may also yield pertinent information on diseases which appear histologically quite similar and may be related, as in other post-vaccinal and post-infectious encephalomyelitis. Its relation to multiple sclerosis and other demyelinating diseases remains to be determined.

Proposed Course of Project: Chemical fractionation of the brain has always been difficult, especially with respect to lipids and proteins, which probably contain the encephalitogenic factor. The opportunity to study histologically the disease produced by relatively precise chemical fractions of the brain is very valuable, not only to check on the occurrence of the disease but also to plan further experiments to determine the way in which the causative agent affects the brain.

9. PROJECT DESCRIPTION: (continued)

In addition, other experiments are planned for histologic study of the earliest sub-clinical lesions and for the study of possible reasons for variation in the susceptibility of individual animals.

R.P.C. 2
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-36 (C)
SERIAL NO.

11. BUDGET DATA

	EST. EXPEND.	BUDGETED POSITIONS PROF.	OTHER	TOTAL	MAN YEARS PROF.	OTHER	TOTAL	PATIENT DAYS
FY 1955	$1,095	1	--	1	0.2	--	0.2	
FY 1956	$1,115	1	--	1	0.2	--	0.2	

12. BUDGET ACTIVITY:

RESEARCH [x] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.

Basic Research Division, National Institute of Mental Health, Dr. Norman Goldstein.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE IDENTIFY SUCH PROJECT.

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-36 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness (INSTITUTE) 2. Surgical Neurology (BRANCH)

3. Clinical Neuropathology (SECTION) 4. _____ (LOCATION) 5. NINDB-37 (C) (SERIAL NO.)

6. Neuropathologic investigations of focal epilepsy and other neurological diseases
PROJECT TITLE

7. Ellsworth C. Alvord, Jr., M. D.
PRINCIPAL INVESTIGATOR

8. Maitland Baldwin, M. D., Kirkland Brace, M. D., and John Lilly, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To determine the histopathologic substrata of focal epileptic seizures in human beings and to determine the morphologic correlates of other neurological disorders in human patients and experimental animals.

Methods Employed: Portions of brain are studied following paraffin or celloidin embedding or frozen sections with specific stains for nuclei, Nissl granules, myelin sheaths, neurofibrilae, axons, neuroglia, and connective tissue. Other techniques for the demonstration of specific enzymes and histochemical materials are being developed.

Patient Material: Patients are obtained through the Surgical Neurology Branch, NINDB. Human brain material is obtained at the time of operation from patients requiring neurosurgical intervention for the treatment of focal epileptic seizures.

Major Findings: 52 brain biopsies have been received during the year, predominately from temporal lobectomies for the treatment of focal epileptic seizures. Unfortunately, due to the shortage of adequately trained technical assistants, only a few of these have been studied. The incidence of neoplasm, gliosis, atrophy or other disease awaits a more thorough examination of these and the other cases. In addition, of approximately 100 autopsies performed at the NIH, 30 have been of sufficient interest for further neuropathologic investigation. Other autopsied cases have been obtained from outside sources, particularly D. C. General Hospital and George Washington University Hospital, where Dr. Alvord conducts regular brain cutting and microscopic review sessions. Of several hundred brains examined during the past year, 50 have been obtained for further neuropathologic investigation. In addition, some three dozen grossly normal brains have been acquired for teaching and gross dissection as well as for normal histologic controls.

The effects of various traumatic agents have also been studied in experimental animals. With Dr. Brace of the National

PROJECT DESCRIPTION: (continued)

Cancer Institute, experiments have been performed to determine the effects of high doses of X-irradiation on the nervous system of guinea pigs. 50 animals have been received for histopathologic study with particular emphasis on changes in the cerebellar granule cells. Interest centers especially about the time course of these changes, their variation with different doses of X-ray delivered to different parts of the head and body, and their modification by drugs such as nembutal. Other experiments are being performed with Dr. Lilly of the National Institute of Mental Health, to determine the relative degree of damage to the cerebral cortex by repetitive electrical stimulation with different wave forms of electrical current. One monkey, after seven weeks of daily prolonged stimulation by electrical currents of special wave characteristics showed moderate gliosis of the cortex with good preservation of neurones. Other animals are now being prepared in an attempt to control the effects of operative trauma and of stimulation by different electrical wave forms to test the hypothesis that repetitive electrical stimulation need not concommitantly destroy neurones. In addition to the above experiments of particular neuropathologic interest, the laboratory has processed material submitted by Dr. Baldwin concerning the amygdaloid nucleus in monkeys, and has received specimens from Drs. Ajmone-Marsan, Shy, and Li. So far 41 cats and monkeys as well as 13 miscellaneous specimens have been received for histologic examination. Unfortunately, much of this material has not been processed due primarily to the prolonged shortage of adequately trained personnel, a deficiency which has only recently been partially corrected.

Significance to Neurological Research: The determination of the precise type and cause of disease of the nervous system associated with focal epileptic seizures is of great importance in the management and treatment of such patients. Since it is thought that many of these patients develop seizures following various traumatic disturbances of brain, either at birth or afterwards, and since, during their neurosurgical operation, the patients are subjected to local electrical stimulation of the brain as part of the investigation of the functional organization of the cerebral cortex and subcortical structures, the experiments in animals provide an excellent opportunity to analyze the methods by which the brain reacts to various injurious agents such as X-irradiation or electrical stimulation. The acquisition and study of brains showing a variety of neurological diseases is considered important, not only for the liaisons with civilian pathologists, but also for the development of a well-rounded neuropathological research program in diseases of the nervous system.

Proposed Course of Project: With the further training of the present technicians, it will be possible to study all of the neurosurgical cases in order to arrive at a diagnosis more quickly so that the treatment of the patients might be benefited. The results of the experiments are also eagerly desired as soon as possible.

R.P.C. 2
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-37 (C)
SERIAL NO.

11. BUDGET DATA

	EST. EXPEND.	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1955	$9,270	2	3	5	0.3	1.4	1.7	
FY 1956	$9,480	2	3	5	0.3	1.4	1.7	

12. BUDGET ACTIVITY:

RESEARCH [x] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.

National Cancer Institute, Dr. Kirkland Brace; and Section on Cortical Integration, National Institute of Mental Health, Dr. John Lilly.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE IDENTIFY SUCH PROJECT.

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-37 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R. P. C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness 2. Surgical Neurology
INSTITUTE LABORATORY OR BRANCH

3. Clinical Psychology 4. _____ 5. NINDB-38(C)
SECTION LOCATION (OTHER THAN BETHESDA) SERIAL NO.

6. The Role of the Temporal Lobe in Perception.
PROJECT TITLE

7. Laurence L. Frost
PRINCIPAL INVESTIGATOR(S)

8. Mildred Blevins, Maitland Baldwin
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

OBJECTIVES: To determine the part played by the temporal lobe in the perception of visual, auditory, and tactual stimuli.

METHODS EMPLOYED:

a. Psychological and neurological tests of perception administered to patients before and after temporal lobe surgery.

b. Conditioning experiments with monkeys and chimpanzees trained in close discriminations.

PATIENT MATERIAL: Temporal lobe seizure patients from Surgical Neurology ward.

Male	21	Adult	25
Female	4	Child	0

MAJOR FINDINGS:

a. Generally speaking, visual perceptual accuracy is somewhat below expectation for a normal group. A rather marked sequence of perceptions of adequate and inadequate quality is noted before operation which is more marked following surgical intervention.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: Perception being a major facet of personality, investigation along this line is necessary to full evaluation of temporal lobe function for the Branch of Surgical Neurology.

NINDB-38 (C)
SERIAL NO.

PROPOSED COURSE OF PROJECT: Continuation of present lines of inquiry modified as further investigation dictates. This project is allied with projects entitled Mechanisms of Memory and Visual Field Defects Following Temporal Lobectomy, Branch of Surgical Neurology.

Budget Data Sheet

10. NINDB-38(C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PAT. DAYS
FY 1955	$2,600	1	1	2	0.3	0.2	0.5	
FY 1956	$2,640	1	1	2	0.3	0.2	0.5	

12. BUDGET ACTIVITY:

RESEARCH (X) ADMINISTRATION ( )

REVIEW & APPROVAL ( ) TECHNICAL ASSISTANCE ( )

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM)

NONE

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTER* CHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

NONE

Honors, AAwards, and Publications Sheet

15. NINDB-38 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

R. P . C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness 2. Surgical Neurology
INSTITUTE LABORATORY OR BRANCH

3. Clinical Psychology 4. _____ 5. NINDB-39(C
SECTION LOCATION (OTHER THAN BETHESDA) SERIAL NO.

6. Function of the Temporal Lobe in the Recording of Experiences.
PROJECT TITLE

7. Laurence L. Frost
PRINCIPAL INVESTIGATOR(S)

8. Maitland Baldwin, Mildred Blevins, Charles Wood
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

OBJECTIVES:
a. To determine the role of the temporal lobe, with its central connections, in learning, recollection, and recall.

METHODS EMPLOYED:

a. Psychological and learning tests administered to patients with temporal lobe epilepsy prior to and following removal of one or the other temporal lobe.

b. Conditioning experiments using monkeys and chimpanzees to be subjected to bitemporal removal.

c. Observation of imitative learning and general retentiveness in infant rhesus monkeys who have had both temporal lobes removed.

PATIENT MATERIAL: Temporal lobe seizure patients from Surgical Neurology ward.

Male	21	Adult	25
Female	4	Child	0

MAJOR FINDINGS:

a. Learning speed and recall ability does not appear greatly affected by a pathological or absent temporal lobe. The greatest deficit to learning and recall appears to be in the area of attenti to task and ability to concentrate. During a few episodes of noticeably active behavior continuing over a period of hours to day and during which the electroencephalogram showed a mild to marked

increase in abnormality in one temporal lobe, recall for the event by the patient appears to bear a direct relationship to the amoun t of the abnormality.

b. Conditioning experiments on monkeys indicated a mild loss in ability to respond to the conditioned stimulus while the amygdaloid nucleus was stimulated electrically.

c. Infant monkeys who have had both temporal lobes removed have learned imitatively from cage mates and have responded to conditioning experiments.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: Patients suffering from temporal lobe seizures frequently complain of memory loss, and their behavior during "automatic" episodes frequently accompaning such seizures is usually lost to them. This project hopes to point the way toward a solution o f this "experience recording" problem. As such it is a large part of the entire program of the Branch of Surgical Neurology

PROPOSED COURSE OF PROJECT: Attempting to develop refined measures of learning and retention to apply to humans. This project is allied with project titled Mechanisms of Memory, Branch of Surgical Neurology.

Budget Data Sheet

10. NINDB-39 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROG	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PAT DAY
FY 1955	$2,600	1	1	2	0.2	0.3	0.5	
FY 1956	$2,640	1	1	2	0.2	0.3	0.5	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]
REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S). (ITEM)

NONE

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

NONE

Honors, Awards, and Publications Sheet

15. NINDB-39 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

R. P. C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness (INSTITUTE) 2. Surgical Neurology (LABORATORY OR BRANCH)

3. Clinical Psychology (SECTION) 4. _____ (LOCATION (OTHER THAN BETHESDA)) 5. NINDB 40 (C) (SERIAL NO.)

6. Speech Areas in Man
PROJECT TITLE

7. Laurence L. Frost
PRINCIPAL INVESTIGATOR(S)

8. Maitland Baldwin
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

OBJECTIVES: Location of brain areas involved in the production and comparison of speech.

METHODS EMPLOYED: Speech testing of conscious patients while the exposed brain is being electrically stimulated.

PATIENT MATERIAL: Temporal lobe seizure patients from Surgical Neurology ward. Male 25 Adult 25 Female 5 Child 2

MAJOR FINDINGS: There has been no gross evaluation of data. Such areas located indicate three major areas motor speech, receptive speech, and expressive speech.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: One of the aims of the Branch is to determine functional localization areas of the brain. This project is designed to give information regarding the areas necessary for comprehension and production of speech.

PROPOSED COURSE OF PROJECT: This project is allied with project titled An Investigation of Speech Function Localized in the Temporal Areas of Man.

Budget Data Sheet

10. NINDB-40 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PAT. DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$2,600	1	1	2	0.3	0.2	0.5	
FY 1956	$2,640	1	1	2	0.3	0.2	0.5	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM)

NONE

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

NONE

R. P. C. - 3
December 1954 Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-40 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

R. P. C. - 1
December 1954 Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness (INSTITUTE) 2. Surgical Neurology (LABORATORY OR BRANCH)

3. Clinical Psychology (SECTION) 4. _____ (LOCATION (OTHER THAN BETHESDA)) 5. NINDB 41 (C) (SERIAL NO.)

6. Personality Characteristics of Temporal Lobe Epileptics. (PROJECT TITLE)

7. Laurence L. Frost (PRINCIPAL INVESTIGATOR(S))

8. Maitland Baldwin, Mildred Blevins, Charles Wood (OTHER INVESTIGATORS)

9. PROJECT DESCRIPTION:

OBJECTIVES:

a. To determine personality characteristics that are common to or frequent in individuals with epilepsy owing origin to one or the other temporal lobe.

b. To determine the possible role played by the temporal lobe in the formation of personality.

c. To determine the personality characteristics of an individual who has had one or both temporal lobes removed.

METHODS EMPLOYED:

a. Psychological tests administered before and after temporal lobe surgery.

b. Observation of primates (monkeys, chimpanzees) before and following removal of the temporal lobe bilaterally.

PATIENT MATERIAL: Temporal lobe seizure patients from Surgical Neurology ward.

Male	22	Adult	25
Female	5	Child	2

MAJOR FINDINGS:

a. Survey of a portion of the material thus far collected indicates three outstanding areas of functioning in these patients that are on the whole different from a random selection of the population:

1. A test involving learning, attention, concentration, visual-motor speed, and memory is constantly and markedly lowered when compared with other testing areas.

2. A test involving appraisal of relationships and visual recognition and identification is most usually high compared with other testing areas as is

3. A test involving judgement.

These several areas when considered together indicate that these individuals may exercise adequate functioning in many areas of personality and of social fitness, however when it becomes necessary for them to carry out these functions in a life situation their performance falls below what would be expected from them.

b. Several infant rhesus macaque monkeys have had their temporal lobes removed bilaterally and as they mature will be compared with contacts of the same age and sex. In the relatively short time since the operation procedures, little or no change is noted.

c. Following removal of one temporal lobe, human patients exhibit an increase in control personality characteristics which existed before operation, but which were not marked. For example, a mildly hostile person before surgery may show a marked increase in behavior best described as demanding. Frequently they are seen to become more out-going, more talkative, and in some cases, seem to desire more physical contact with their environment. Primate studies here are indicated in b.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: As psychological alterations in temporal lobe seizure patients are one of the outstanding features recognized by investigators in this area, the significance is rather large.

PROPOSED COURSE OF PROJECT: A continuation of present lines of investigation only as modified by thorough evaluation of all data as given during the present calendar year. This project is allied with project entitled Mechanisms of Memory, Branch of Surgical Neurology.

Budget Data Sheet

10. NINDB-41 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PAT. DAYS
FY 1955	$2,630	1	1	2	0.2	0.3	0.5	
FY 1956	$2,650	1	1	2	0.2	0.3	0.5	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM)

NONE

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

NONE

R. P. C. - 3
December 1954 Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-41 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Surgical Neurology — BRANCH
3. Neurosurgical Service — SECTION
4. _____ — LOCATION
5. NINDB-42 (C) — SERIAL NO.
6. Hearing deficits following temporal lobectomy — PROJECT TITLE
7. John T. Lord, M. D. — PRINCIPAL INVESTIGATOR
8. Maitland Baldwin, M. D. and Paul Chatfield, M. D. — OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: To elucidate the relative importance of the left and right audito-receptive cortex of the temporal lobes of man in hearing.

Methods Employed: Pre- and postoperative audiometry in patients subjected to temporal lobectomy for cerebral seizures.

Patient Material: Adult males: 4
Adult females: 3

Major Findings: In contradistinction to previous reports, there is suggested evidence that complete resection of a single temporal lobe may result in significant hearing loss. It is further tentatively suggested that resection of the dominant temporal lobe, when followed by a receptive type of aphasic disorder, results in a marked bilateral hearing loss.

Significance to Neurological Research: The functional role of the auditory pathways may be more clearly elucidated, thereby facilitating neurological diagnosis in temporal lobe lesions, both from the standpoint of localization and lateralization. It is hoped that the deafness following dominant hemisphere resection may be established to be in part responsible for the receptive aphasic disorder and that re-education of the speech function may be more readily accomplished with suitable sound-amplifying devices.

Proposed Course of Project: Detailed pre- and postoperative audiometric studies will be carried out on all patients to be subjected to temporal lobectomy in treatment of cerebral seizures. If practicable, audiometry will be performed in the human operating room in the course of temporal resection, as an adjunct to speech testing.

R.P.C. 2
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-42 (C)
SERIAL NO.

11. BUDGET DATA

	EST. EXPEND.	BUDGETED POSITIONS PROF.	OTHER	TOTAL	MAN YEARS PROF.	OTHER	TOTAL	PATIENT DAYS
FY 1955	$3,000	3	--	3	0.9	--	0.9	
FY 1956	$3,050	3	--	3	0.9	--	0.9	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE IDENTIFY SUCH PROJECT.

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-42 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Special U. S. Public Health Service Fellowship in Neurophysiology

R.P.C. 1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Surgical Neurology — BRANCH
3. Neurosurgical Service — SECTION
4. _____ — LOCATION
5. NINDB-43 (C) — SERIAL NO.
6. Vestibular representation in the temporal lobe — PROJECT TITLE
7. John T. Lord, M. D. — PRINCIPAL INVESTIGATOR
8. Maitland Baldwin, M. D. and Paul Chatfield, M. D. — OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: To provide further information concerning the influence of the intact temporal lobe upon vestibular reflexes in postural and ocular adaptation.

Methods Employed: 1. Measurement of nystagmoid preponderance following caloric stimulation in patients subjected to temporal lobectomy for treatment of cerebral seizures.
2. Measurement of postural disturbances and adaptation to same following caloric irrigation in a similar group of patients.

Patient Material: Adult Males: 11
Adult Females: 7

Major Findings: Nystagmoid preponderance was, in general, lateralized to the side of the lesion and was accentuated both with respect to the intact and to the operated hemisphere. The first group of ten patients was examined using subjective vertigo as the index of preponderant vestibular disturbance. This was found to be an unreliable method of examination. Chronic studies up to six months following an anatomically controlled temporal resection show inconsistencies in the lateralization of the preponderance, suggesting that the preoperative lesions which were of a chronic nature could not be lateralized reliably without refinements in this technique. In a smaller group of patients postural disturbances were recorded cinematographically with a special apparatus.

Significance to Neurological Research: If it is felt that this method is sufficiently reliable and if further consistencies appear between both the lateralization and the localization of the confirmed lesion and the preponderant vestibular disturbance, the method will be of considerable value in the localization of cerebral damage and will further the efficiency by which epileptogenic foci are localized.

PROJECT DESCRIPTION (continued)

Proposed Course of Project: At present there is no evidence supporting the claim of Halpike and Carmichael that the center for calorically induced nystagmus occupies the posterior temporal region only. Pre- and postoperative studies of nystagmoid preponderance and postural disturbance and adaptation will be carried out in patients suffering from temporal lobe epilepsy.

R.P.C. 2
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-43 (C)
SERIAL NO.

11. BUDGET DATA

	EST. EXPEND.	BUDGETED POSITIONS PROF.	OTHER	TOTAL	MAN YEARS PROF.	OTHER	TOTAL	PATIENT DAYS
FY 1955	$3,000	3	--	3	0.9	--	0.9	
FY 1956	$3,050	3	--	3	0.9	--	0.9	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE IDENTIFY SUCH PROJECT.

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-43 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Special U. S. Public Health Service Fellowship in Neurophysiology

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Ophthalmology — LABORATORY OR BRANCH

3. Clinical — SECTION
4. _____ — LOCATION (IF OTHER THAN BETHESDA)
5. NINDB-44(C) — SERIAL NO.

6. The Pathogenesis and Treatment of Granulomatous Uveitis — PROJECT TITLE

7. Ralph W. Ryan, M.D. — PRINCIPAL INVESTIGATOR(S)

8. John J. Culligan, M.D.; James F. O'Rourke, M.D.; Gilbert Iser, M.D.; Leon Jacobs, Ph.D., NMI. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

"Uveitis", or non-purulent inflammation of the uveal tract, takes one of two clinical forms: (1) a "non-granulomatous" type, which is thought to represent a hypersensitive state to bacterial products, and (2) a "granulomatous" type, which is due to direct invasion of the uveal tract by the infecting organism. Of the granulomatous variety, many cases formerly thought to be tuberculous in origin have been shown recently to be due to infection with a parasite which morphologically resembles Toxoplasma. Because in cases of congenital toxoplasmosis, uveitis is a most common finding, the parasite found in adult eyes is presumptively also Toxoplasma. The question of its identity has been raised, however, by several workers on the basis of the similarity of serological survey results on groups of individuals with and without eye disease. The identification of the organism depends on adequate study of a large number of cases which have been given exhaustive medical study and, if possible, on the investigation of parasites isolated from the eye, should the opportunity arise.

Objectives: To improve diagnostic methods in relation to granulomatous uveitides.

To determine etiological factors involved in causation of granulomatous uveitis more definitively than they are presently known.

To discover new causative agents in this disease if possible. Particularly to evaluate the incidence of toxoplasmosis as a causative factor.

To evaluate treatment regimens in granulomatous uveitis, and in particular in toxoplasmic uveitis.

Methods employed: Referred patients with a diagnosis of acute or chronic granulomatous uveitis will be accepted for admission to the Clinical Center. Where practical the treatment ordered by the referring physician will be continued while the patient undergoes diagnostic studies either as an in-patient or out-patient.

The patient will be studied by careful history and clinical evaluation, X-rays, laboratory tests, intradermal tests, special examinations of various types as they may be indicated, to determine the presence of systemic manifestations of disease. Thorough ocular examination will be carried out, using the best instruments available and such techniques as ophthalmoscopy, biomicroscopy, refraction and gonioscopy.

Since toxoplasmic uveitis is of special interest in this study, every effort will be made to exclude other known possible causes of uveal tract disease to strengthen presumptive diagnoses of toxoplasmic uveitis from such evidence as positive methylene blue dye tests and positive toxoplasmin tests.

Specimens of aqueous, vitreous, or other material taken from eyes by paracentesis or after enucleation will be examined by various laboratory techniques to identify etiological agents where feasible.

Active cases presumed due to Toxoplasma gondii will be treated by permission of the referring physician, using such agents as pyrimethamine, the sulfa drugs, corticosteroids, passive antibody transfer and others which may appear logical or promising. Cases due to other causes may be treated if of research interest, if agreeable to the referring physician.

Animal experimentation will be used both in advancing diagnostic methods and treatment regimens wherever such studies appear rational and useful.

Patient Material: Granulomatous uveitis cases obtained by physician referral.

Major Findings in 1954: A report was presented to the September 1954 annual meeting of the American Academy of Ophthalmology on the incidence of presumptive cases of toxoplasmic uveitis among the cases seen here. The paper also described the therapeutic results and side effects on the active cases treated with pyrimethamine and sulfas.

A report was delivered by Doctor Leon Jacobs of the National Microbiological Institute at the September meeting of the International Congress of Ophthalmology. This concerned production of experimental anterior granulomatous toxoplasmic uveitis in rabbits. The value of this technique is in obtaining a suitable uniform animal preparation with which to test the value of treatments, as well as to observe the course of proven toxoplasmic uveitis.

It seems convincingly shown that one may use the diagnostic methods previously described to arrive at acceptable presumptive diagnoses of toxoplasmic uveitis. Active cases may be expected to show therapeutic response to treatment with pyrimethamine and sulfadiazine.

Significance of Program: Uveitis may be responsible for as much as from 10% to 15% of blindness in adults. From 25% to 50% of such cases may be due to the Toxoplasma. The findings in regard to diagnosis and treatment thus assume considerable importance to ophthalmologists. It is of considerable value to the Institute to have so quickly achieved some pre-eminence in this phase of ophthalmic research.

Proposed Course of Project: The study of toxoplasmic uveitis has been divided logically into three phases. The first, concerning an acceptable method of diagnosis and a successful therapeutic regimen has been completed.

A second phase was formulated to determine the best regimen of pyrimethamine and sulfa drugs to use in therapy. Determination of pyrimethamine levels in body fluids and tissues is a necessary factor in this phase of study.

The third phase would be the evaluation of adjuvant therapy for use with pyrimethamine and the sulfa drugs. Corticosteroids and passive antibody transfer are examples of adjuvant therapy logically requiring evaluation.

Present status: Phase one has been reported on. Active cases are available for treatment. However, Phase 2 has been held up since September because of unavailability of determinations of body fluid pyrimethamine levels. An attempt to solve this problem by filling the vacancy for a pharmacologist on the Eye staff was rejected by the Institute Director. No laboratory facilities have been made available to the Ophthalmology Branch for this work, though an improvised laboratory was tentatively arranged in the in-patient eye clinic for the use of a pharmacologist to begin this work.

R.P.C. 4
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-44 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$25,000	4	3	7	1.5	1.2	2.7	
FY 1956	$26,800	4	3	7	1.5	1.2	2.7	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICIAN ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1).

Dr. Leon Jacobs of the National Microbiological Institute, Laboratory of Tropical Diseases, is carrying on animal, tissue culture, and epidemiological investigation of Toxoplasma gondii in collaboration with our Branch. He furnishes facilities and supervision for the methylene blue dye test and the complement fixation test and prepares toxoplasmin antigen for clinical use. Miss M. K. Cook who performs the dye tests is furnished all needed facilities and supervision in Doctor Jacobs' laboratory.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:(BY SERIAL NO(S) IF WITHIN NIH).

This complements animal experimentation carried on by Dr. Don Eyles at the Memphis Public Health Service facility.

R.P.C.-5
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-44 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

1. Ryan, R.W.; Hart, W.M.; Culligan, J.J.; Gunkel, R.D.; Jacobs, L.; and Cook, M.K. Diagnosis and Treatment of Toxoplasmic Uveitis. Trans. Amer. Acad. Ophth. and Otol., Nov.-Dec. 1954.

2. Jacobs, L.; Hart, W.M.; Ryan, R.W.; and Cook, M.K. The Production of Experimental Ocular Toxoplasmosis in Rabbits. Proœedures of the XVII Internat'l. Cong. Ophth. Sept. 1954.

3. Jacobs, L.; Ryan, R.W.; Cook, M.K.; and Hart, W.M. Toxoplasmosis. a common infection. (a brochure prepared for distribution with Exhibit in 4.)

4. Exhibit. Toxoplasmosis. A common infection. XVII Internat'l. Congress of Ophthalmology and American Academy of Ophth. and Otol., New York, Sept. 1954.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C. 1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Ophthalmology — LABORATORY OR BRANCH

3. _____ — SECTION
4. _____ — LOCATION (IF OTHER THAN BETHESDA)
5. NINDB-45 (C) — SERIAL NO.

6. The Effect of Administration of Certain Amino Acids on the Course of Familial Pigmentary Degeneration of the Retina (Retinitis Pigmentosa) — PROJECT TITLE

7. Ralph W. Ryan, M.D. — PRINCIPAL INVESTIGATOR(S)

8. John J. Culligan, M.D.; James F. O'Rourke, M.D. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

In the absence of definite proof as to whether the degeneration of neural cells or vascular channels is the primary process, it appears logical that the chance of retarding or arresting the degenerative process by providing better nutrition of neural tissue should be investigated. Doctor Donald Tower's work suggests accomplishment of this by oral use of l-asparagine.

Objectives: To test the effect of such drugs as levo-asparagine and glutamic acid on clinical cases of retinitis pigmentosa to see whether retardation, arrest, or regression of the degenerative process can thus be accomplished.

Methods employed: Careful ocular examinations with frequent charting of the visual fields to determine changes of small degree while being treated over a period of months with the chosen amino acid substance.

Patient Material: A small number of selected patients with typical retinitis pigmentosa, preferably very early in the degenerative process, will be accepted on referral by physicians.

Major Findings in 1954: On two patients on treatment for a relatively short period of months, no significant change was observed in ocular findings.

Significance to Institute Program: Retinitis pigmentosa is a representative of a number of degenerative diseases of the retina responsible for a significant percentage of the cases of severe visual loss in adults.

Proposed Course of Project: The most desirable cases to test this treatment are very difficult to find. Since the drugs are very expensive, it is felt that a preliminary trial should be limited to a very small number of patients who as nearly as possible fulfill our criteria. Treatment on these should be continued long enough for further degeneration to have been measurable if untreated.

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-45 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	BUDGETED POSITIONS OTHER	BUDGETED POSITIONS TOTAL	MAN YEARS PROF	MAN YEARS OTHER	MAN YEARS TOTAL	PATIENT DAYS
FY 1955	$21,300	3	3	6	1.1	1.2	2.3	
FY 1956	$23,000	3	3	6	1.1	1.2	2.3	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICIAN ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

This project might be considered complementary to the project on control of epilepsy under supervision of Doctor Donald B. Tower.

R.P.C. 4
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-45 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Ophthalmology — LABORATORY OR BRANCH

3. _____
4. _____ — LOCATION (IF OTHER THAN BETHESDA)
5. NINDB-46(C) — SERIAL NO.

6. Chemical and Physical Changes in Lenticular Cataract Formation - Clinical Phase — PROJECT TITLE

7. Ralph W. Ryan, M.D. — PRINCIPAL INVESTIGATOR(S)

8. James F. O'Rourke, M.D.; William M. Hart, M.D.; Gilbert Iser, M.D.; and John J. Culligan, M.D. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Previous attempts to elucidate the pathogenesis of cataract have been fraught with the difficulty that isolated lenses were subjected to chemical or physical analysis without regard to changes in composition as a function of growth and aging. Since these changes are known to be of considerable magnitude, chance analysis cannot be expected to be fruitful in establishing a pattern of chemical derangement in cataract. The clinical approach to this problem must be supplemented by animal material in which it is possible to obtain rigorous control of all variables.

Objectives: To furnish clinical and biophysical portion of a study of the mechanism of cataract formation in collaboration with a biochemical study (described on a separate form).

To attempt identification of the lenticular changes primarily associated with growth, maturation and physiological aging.

To furnish human lenses from intracapsular cataract extraction and from autopsy material to use in chemical study.

To test the value of any suggested measures for cataract prevention on experimental animals, and if safe and feasible, on a clinical basis.

Methods: Maturation and aging changes in the lens will be studied on experimental animals of a wide range of known ages from conception. Biophysical properties will be recorded and lenses turned over to the Biochemical laboratory for chemical studies. Human lenses from intracapsular cataract extraction and from autopsies will be studied for correlation with the animal lenses in regard both to age physical changes and the chemical changes.

Animal experimentation will be conducted wherever useful to test laboratory findings and to test suggested measures calculated to prevent cataract formation or progression.

Patient Material: Patients referred to the Clinical Center for cataract extraction and ocular specimens obtained at autopsy or from radical tumor surgery.

Major Findings: None to date.

Significance to Institute Program: Cataract is one of the important causes of visual loss, especially in the aged. With radiation becoming an increasing hazard, the prevention of cataract assumes a tremendous significance.

Proposed Course: The biochemical phase of this project may well set the pace for clinical activity. The biophysical studies of animal lenses should be carried out as soon as laboratory facilities permit. Then human lens material should be amassed as the general clinical activity of the Ophthalmology Branch permits.

Animal studies may be set up as required by laboratory developments.

During 1954 a number of cataractous lenses were obtained. These were quick-frozen and are being held until needed by the biochemical laboratory for studies.

R.P.C. - 3
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-46 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$32,400	5	4	9	1.9	1.6	3.5	
FY 1956	$35,000	5	4	9	1.9	1.6	3.5	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICIAN ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1).

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH).

R.P.C. - 4
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-46 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS, AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C.-5
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Ophthalmology — LABORATORY OR BRANCH

3. _____ — SECTION
4. — LOCATION (IF OTHER THAN BETHESDA)
5. NINDB 46 (C) — SERIAL NO.

6. Chemical and Physical Changes in Lenticular Cataract Formation - Biochemical Phase
PROJECT TITLE

7. Robert A. Resnik, Ph.D.
PRINCIPAL INVESTIGATOR(S)

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

The lens of the eye is composed of water and protein. It is reasonable to suppose that clouding of this structure, which we refer to as cataract, is the result of changes in this protein-water system. It has been shown that analogous proteins undergo changes in optical properties as a result of "denaturation" of the protein molecule. The earliest chemical alteration in such a process involves the release of a sulfhydryl group from the protein molecule. It is of interest that the lens contains the highest concentration of sulfhydryl groups of any tissue in the body. There are many means by which experimental cataract can be produced in the intact animal, and they all have in common a loss of sulfhydryl substance from the lens. Since enzymes are composed of proteins, it is not surprising that alterations in oxidative processes accompany the development of cataract. It is not known if these effects are primary or secondary to the general change in protein structure.

Objectives: To furnish biochemical correlation with the clinical and biophysical phase of this project (described on separate form).

To determine the biochemical mechanism of cataract causation.

To help identify the lenticular changes associated with growth, maturation and physiological aging.

To determine the mechanisms involved in lenticular opacification caused by so-called cataracto-genic agents such as alloxan.

Study of mechanism of lens opacification from any endogenous or exogenous cause which may be expected to increase our understanding of the general process.

Two units of investigative work have been organized. Their specific objectives are as stated below:

Unit 1.- To study the affinity of alloxan for various inorganic cations.

Unit 2.- To determine whether the interaction between alloxan and polypeptides is entirely dependent on sulfhydryl groups.

Methods: Biochemical studies will be conducted to determine the mechanism of action of drugs and other agents known to produce experimental cataracts. In this way it is hoped that clues will be discovered pointing to the initial biochemical events leading to the development of lens opacification. The interrelation of ocular enzyme systems and lens protein under the action of these cataractogenic influences will be investigated on animal material.

Animal and human lenses of known age will be examined chemically to determine changes which appear to associate with growth, maturation and physiological aging and also those associated with cataract formation.

Agents which counteract or prevent the deleterious effects of cataractogenic agents will be studied to determine mechanism of action. Measures showing any promise in prevention of cataract formation will be tested in animals and considered for possible clinical tests by the clinical group.

Methods employed in the units of investigation being carried out now include such procedures as absorption spectrophotometry, pH determination, low temperature centrifugation, and synthetic reactions.

Major Findings: The specific units investigated thus far have revealed the following:

Unit 1.- The formation of an alloxan-iron complex in alkaline solutions has been confirmed.

In acidic solutions alloxan will form blue complex with iron provided phosphate is present.

Cobalt and alloxan form a purple complex upon the addition of base.

Both the cobalt and iron complexes do not lend themselves to recrystallization.

Nickel appears to form a complex with alloxan as evidenced by a slight shift of the absorption spectrum.

Ammonia does not interfere with the formation of these complexes.

Unit 2.- It has been confirmed that alloxan does react with sulfhydryl groups as evidenced by reactions with reduced glutathione and thioglycolic acid.

The spectrum of the thioglycolic acid-alloxan adduct is shifted by glycylglycylglycine and glycylglycine but not by glycine itself.

There is no evidence to confirm the reports of spectrophotometric evidence for the interaction between alloxan and sulfhydryl

groups of denatured bovine serum albumin, denatured ovalbumin, and native urease.

Significance: Cataract is one of the important causes of visual loss, especially in the aged. With radiation becoming an increasing hazard, the prevention of cataract assumes a tremendous significance.

The significance of the units of investigation in progress may be summarized as follows:

Unit 1.- The current observations in the laboratory seem to indicate that alloxan may very well be toxic to physiological systems by complexing with various essential co-factors.

This would obviate the necessity for concluding that alloxan is physiologically a toxic agent solely because of its affinity for sulfhydryl groups.

Unit 2.- The significance of this work lies in the important but as yet incompletely defined, role of sulfhydryl groups in proteins, Further, while it was not our original intention to disprove the evidence in the literature which attributes the physiological effects of alloxan to reaction with sulfhydryl groups, it appears at this point that there must be in part, if not entirely, another means by which alloxan produces the physiological manifestations that it does.

Proposed Course: The project should be continued as planned with whatever modification appears logical from the developments of the investigation.

In regard to the units under investigation, it is proposed that in Unit 1 we continue our current investigation of alloxan-cation complexes. The chemical behavior of alloxan and quinones will be compared since the properties of the complexes of these two substances are similar.

In Unit 2 we propose continuation of the current efforts to identify the reaction product of the reaction between glutathione and alloxan. It is also our desire to determine, if possible, what the nature of the spectral shift is due to in the presence of glycylglycine and diglycylglycine.

Progress Report: The biochemical laboratory was organized late in 1954 and therefore studies were carried on for less than half of the calendar year.

Progress on the two units of investigative work being carried on up to this time is described below:

The goal originally set forth in this laboratory was to determine whether the physiological effects of alloxan are entirely dependent on sulfhydryl groups.

The avenues by which alloxan may produce diabetes and the ensuing lenticular opacities are many indeed. Since alloxan inhibits enzyme systems we undertook an investigation of the reaction of alloxan with proteins and peptides with specific interest in those proteins and peptides containing sulfhydryl groups.

Evidence in the literature that alloxan combines with sulfhydryl groups of proteins was not confirmed. No specific maximum was observed in the absorption spectra of alloxan with proteins containing free sulfhydryl groups. Using glutathione and thioglycolic acid it was found that alloxan does affect -SH groups. It does not seem likely, however, that alloxan itself combines with these compounds since this would require the confirguration of a quinone.

The results obtained thus far seem to coincide in principle with findings in other laboratories that suggest some mechanism other than combination with -SH groups.

Viscosimetric studies also give no reason to believe that alloxan may combine with proteins.

Since metals are co-factors or mediators in a great many enzymatic systems the interaction of alloxan with cations lends itself to this problem of the mechanism of the action of alloxan on physiological systems.

It has been found that alloxan forms complexes with iron, cobalt, and possibly nickel. Alloxantin, which exists only in the crystalline state and forms an equilibrium mixture of alloxan and dialuric acid in solution, also forms a complex with iron.

Experiments intended to identify directly or indirectly the metal complexes of alloxan are planned. In addition those transformations of peptides and polypeptides effected by alloxan will be studied.

R.P.C.- 9
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-46 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$32,400	5	4	9	1.9	1.6	3.5	
FY 1956	$35,000	5	4	9	1.9	1.6	3.5	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION. [ ]

REVIEW & APPROVAL [ ] TECHNICAN ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH)

R.P.C. - 10
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-46 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Ophthalmology — LABORATORY OR BRANCH

3. _____ — SECTION
4. _____ — LOCATION (IF OTHER THAN BETHESDA)
5. NINDB-47 (C) — SERIAL NO.

6. The Penetration into and Distribution of Radioactive Cortisone and Hydrocortisone in the Ocular Tissues — PROJECT TITLE

7. Ralph W. Ryan, M.D. — PRINCIPAL INVESTIGATOR(S)

8. William M. Hart, M.D.; James B. Wyngaarden, M.D. (NHI); Robert A. Resnik, Ph.D. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To obtain data on the penetrability of experimental animal corneas by cortisone and hydrocortisone given by instillation in the conjunctival sac under a variety of regimens.

To obtain data on the distribution of cortisone and hydrocortisone in the various ocular structures and divisions after it has penetrated the cornea or been introduced into the anterior chamber of experimental animals.

To determine whether measurable quantities of cortisone or hydrocortisone reach the choroid and retina of experimental animals from topical instillation or even after single injections into the anterior chamber.

Methods Employed: Radioactive cortisone and hydrocortisone will be administered to rabbits by topical instillation into the conjunctival sac in various concentrations and frequencies, some of which simulate those employed in treatment of clinical patients. The animals will be sacrificed, the eyes removed and dissected for analysis. Following ashing of the tissues and isolation of the C-14 as carbonate, counts of the radioactivity will be made in a suitable device for such measurement.

Similar studies will be made on animal eyes in which a single measured injection of radioactive cortisone or hydrocortisone has been made into the anterior chamber or bulbar conjunctiva.

The extent of testing will be limited by scarcity and cost of the drugs.

Major Findings in 1954: A portion of this project now completed strongly suggests that cortisone and hydrocortisone penetrate the cornea and can be found in the corneal tissue, aqueous, iris and ciliary body in measurable quantities. However, under conditions of the experiments, they did not reach the posterior ocular segment in measurable quantities.

Significance: Cortisone has proved to be an extremely important drug in ophthalmology, and probably represents the most important addition to our therapeutic armamentarium since the introduction of penicillin. It does not appear to have a specific effect upon disease process anywhere in the body, but exerts its action by blocking the responses of the tissues to inflammation. The production of inflammatory exudates and residues in the eye leads to such undesirable sequellae as clouding of the media, complicated cataract, and secondary glaucoma. Cortisone is capable of blocking these responses while the tissues are undergoing recovery either in a spontaneous way or with the help of other therapeutic agents. Locally administered cortisone is efficacious in treating disease process affecting the anterior segment of the eye. So far as is known at present it appears necessary to administer the drug systemically in order to influence inflammatory process in the posterior segment of the eye. It is desirable to determine, therefore, how much cortisone arrives in the posterior segment as a result of local administration and what effect may be produced on this distribution by inflammation of the uveal tract.

Proposed Course of Project: It is desired to use the rest of our small supply of these drugs in the manner previously outlined. If more drugs are available the number of conditions of testing will be increased and systemic injection of the drug will be carried out.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-47 (C)
SERIAL NO.

11. _____
BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$18,500	3	2	5	1.2	0.8	2.0	
FY 1956	$20,000	3	2	5	1.2	0.8	2.0	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICIAN ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

R.P.C. - 4
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-47 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C. - 1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Ophthalmology — LABORATORY OR BRANCH

3. _____ 4. _____ LOCATION (IF OTHER THAN BETHESDA) 5. NINDB-48 (C) SERIAL NO.

6. Study of Adenoidal-Pharyngeal-Conjunctival Virus Conjunctivitis and Associated Disease — PROJECT TITLE

7. Ralph W. Ryan, M.D.; Robert J. Huebner, M.D.; Joseph A. Bell, M.D.; AND Robert H. Parrott, M.D. — PRINCIPAL INVESTIGATOR(S)

8. James F. O'Rourke, M.D. and Gilbert Iser, M.D. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To study the ocular findings associated with the A.P.C. viruses in humans. These viruses were first isolated and identified by Doctor Robert J. Huebner of the National Microbiological Institute in 1953 from adenoid tissue taken from Tonsillectomy and Adenoidectomy surgical cases.

To study clinical manifestations of systemic disease associated with A.P.C. viruses.

To study the growth and antigenic characteristics of the A.P.C. viruses.

To study the epidemiology of the A.P.C. viruses.

Methods Employed: This is a collaborative project with the National Microbiological Institute, all phases of the disease entity being studied concurrently. Our phase is primarily to observe the ocular manifestations in as many patients as can be seen, to obtain conjunctival smears and scrapings for examination and culture, and to assist in gaining information on other phases, such as the epidemiological. Conjunctival exudate will be studied for presence and nature of bacterial organisms, presence and type of white blood cells, presence of inclusion bodies in epithelial cells, and presence and type of A.P.C. virus as shown by tissue culture.

Major Findings in 1954: The association of the A.P.C. viruses with human disease was demonstrated when cultures of type 3 of the virus were isolated from a conjunctivitis case in our out-patient eye clinic in February. Other cases of conjunctivitis combined with pharyngitis and such systemic manifestations as fever, malaise, headaches, muscle pains and gastrointestinal disturbances were found by the Institute of Microbiology staff. An epidemic of the disease occurring in Arlington and spreading through the Washington area gave an opportunity to study all the aspects in some detail. All but one of the cases of conjunctivitis studied here were associated with type 3 of the virus. The one other case was type 4; 6 types of viruses have been identified so far.

Significance to Institute Program: The virus disease described has not been noted to cause permanent visual impairment. However, both the ocular and systemic manifestations have accounted for considerable morbidity in both children and adults during the epidemic noted. There is reason to believe that the disease is common and spreads slowly through a population, only reaching epidemic proportions when some favorable avenue of dissemination such as a children's swimming pool facilitates spread of the virus.

Patient Material: Active cases of conjunctivitis referred to us by physicians.

Proposed Course: To continue seeing referred cases and following the presently outlined objectives until the disease is fully understood and control measures developed.

Permission has been requested to present a collaborative report on the studies on A.P.C. virus disease before the annual meeting of the Ophthalmology Section of the American Medical Association in June. Space has been requested for an exhibit at the annual meeting of the American Academy of Ophthalmology and Otolaryngology in Chicago in October.

R.P.C. - 3
Dec. 1954

Analysis of Program Activities

Budget Data Sheet

10. NINDB-48 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$18,500	3	2	5	1.2	0.8	2.0	
FY 1956	$20,000	3	2	5	1.2	0.8	2.0	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1).

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH (BY SERIAL NO(S) IF WITHIN NIH).

The National Microbiolobical Institute has a program of study integrated with that of the Ophthalmology Branch.

R.P.C. 4
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-48 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

"New Type of Virus Conjunctivitis Described", published in The Sight-Saving Review, Winter, 1954.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C.- 1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Ophthalmology — LABORATORY OR BRANCH

3. _____ — SECTION
4. _____ — LOCATION (IF OTHER THAN BETHESDA)
5. NINDB-49 (C) — SERIAL NO.

6. Evaluation of Electroretinography as a Useful Clinical Tool — PROJECT TITLE

7. Gilbert Iser, M.D. — PRINCIPAL INVESTIGATOR(S)

8. James F. O'Rourke, M.D. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: The measurement of electric potentials from the retina is still primarily in the realm of basic physiologic investigation. Various types of electrodes and stimulating and recording techniques have been used primarily in an attempt to investigate the normal electroretinogram. Up to now what little work has been done on patients with ocular disease has shown little correlation between pathology and abnormal electroretinograms except in conditions such as retinitis pigmentosa and retinal detachment.

We plan to study electroretinograms in cases of intra-ocular pathology in an attempt to determine if there are typical changes with specific disease states, or to show to our satisfaction that with present methods and instruments there are no typical changes and, hence, little clinical usefulness in the procedure.

Methods: The equipment being assembled for use includes (1) a corneal electrode imbedded in a contact lens; (2) a photostimulator (Grass) to serve as a control variable light source; and (3) an eight-channel (Grass) electroencephalograph machine (made available for our use by the Neurology Division) to serve as amplifier and recorder. This equipment is to be standardized at first on a series of normal patients and then used in the pathologic study. It is planned to study each patient under conditions of varying light adaption and photic stimulation.

Patient Material: Studies are to be carried out on both in- and out-patients exhibiting hereditary, inflammatory, and vascular retinopathies. It is expected that we will procure at least part of these patients from collaborative clinics at Howard University and the rest referred from other Institutes and private physicians.

Major Findings: The equipment is now being assembled preparatory to starting our observations. We have consulted with workers in this field at Walter Reed Army Medical Center and the New York Eye and Ear Infirmary about their methods and findings in an attempt to organize our ideas on procedure.

Significance: If typical changes are found associated with ocular disease, the electroretinogram may become another diagnostic and prognostic tool for the ophthalmologist in a field where such a tool would be most valuable. This would be of special importance in cases where opacities prevent adequate visualization of the internal structures of the eye. This program will also fit into complicated glaucoma, cataract and strabismus studies to be undertaken by the Institute.

R.P.C.-3
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-49 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$10,200	2	1	3	0.7	0.4	1.1	
FY 1956	$11,000	2	1	3	0.7	0.4	1.1	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICIAN ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

R.P.C. - 4
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-49 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C. 1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Ophthalmology — LABORATORY OR BRANCH

3. _____ — SECTION
4. _____ — LOCATION (IF OTHER THAN BETHESDA)
5. NINDB-50 (C) — SERIAL NO.

6. Tonographic Studies in Glaucoma
PROJECT TITLE

7. Gilbert Iser, M.D.
PRINCIPAL INVESTIGATOR(S)

8. James F. O'Rourke, M.D.; John J. Culligan, M.D.; Ralph W. Ryan, M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To determine the influence of environmental factors and physiologic alterations on results obtained on tonographic examination of normal persons.

To determine these influences on patients with various types of glaucoma.

To study the outflow mechanism in fresh cadaver eyes with direct manometric checks, both for purposes of minimizing enviromental and physiological influences and of checking calibration of the Mueller tonometer.

To aid in evaluation of effectiveness of various types of glaucoma filtration operations and techniques.

Methods employed: Tonographic measurements will be made on fresh cadaver eyes with direct manometer readings being taken simultaneously to calibrate the tonometer. Similar studies without the manometer can show the outflow characteristics of these eyes.

Tonographic measurements with automatic recording will be performed on normal patients to determine the variations associated with such physiological changes as blood pressure, pulse pressure, degree of hydremia, changes in autonomic activity and the normal diurnal

Similar studies will be made on patients with chronic primary glaucoma. Narrow angle glaucoma cases will be checked during remission to see if their findings differ from the previously studied normals. Secondary glaucoma cases will also be studied. Glaucoma surgical cases will be studied before and after surgery to determine relative effects of different types of filtration operations.

Patient Material: Normal patients will be obtained from other institute referrals and from our own cases in for other types of studies. Glaucoma patients will be obtained from institute referrals to some extent, but primarily from a collaborative glaucoma clinic now in progress at Freedmen's Hospital of Howard University.

Major Findings in 1954: The equipment for this study is not yet complete. However a few patients with questionable diagnosis of chronic primary glaucoma were checked with the Mueller tonometer by hand recording. This resulted in clarifying some doubtful glaucoma diagnoses, some being verified and others disproven.

Significance to Institute Program: Glaucoma is a disease which is characterized by an abnormally high pressure inside the eye. The effect of this abnormal pressure is to diminish the flow of blood to the eye so that the cells of the retina die from lack of oxygen and nutrition. It is thought that this anomaly is due to a blockade of the normal fluid traffic within the eye - specifically an interference with the rate at which fluid leaves the eye. By placing an instrument on the surface of the eye it is possible to obtain an indirect measure of the pressure within the eye and such an instrument is now in routine clinical usage. More recently studies have been conducted in which the instrument is held on the eye for a period of several minutes so as to determine the rate at which the pressure may drop in response to an outside force. The rate at which the pressure drops is thus a measure of the facility with which fluid is able to escape from the eye. It has been found that the exit of fluid is impeded in the glaucomatous eye as compared to the normal eye. This technique has obvious possibilities as a tool in the diagnosis of doubtful cases of glaucoma and as a means of prognosis in determining the response to medical treatment.

Proposed Course of Project: To continue present plans as described but at a rate which will permit other projects to be carried on simultaneously.

R.P.C. - 3
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-50 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$25,900	4	3	7	1.6	1.2	2.8	
FY 1956	$28,000	4	3	7	1.6	1.2	2.8	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICIAN ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S) (ITEM 1).

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R.P.C. 4
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-50 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C. -1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Ophthalmology — LABORATORY OR BRANCH

3. _____ — SECTION
4. _____ — LOCATION (IF OTHER THAN BETHESDA)
5. NINDB-51(C) — SERIAL NO.

6. Evaluation of Certain Techniques in the Diagnosis and Management of Muscular Anomalies of the Eye — PROJECT TITLE

7. Gilbert Iser, M.D. — PRINCIPAL INVESTIGATOR(S)

8. James F. O'Rourke, M.D.; John J. Culligan, M.D.; Ralph W. Ryan, M.D.; and Nancy L. Roberts, Orthoptic Technician. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To obtain comparative data on results obtained from two present methods of management of strabismus cases:

(a) Cycloplegic correction of refractive defects, occlusion of dominant eye, and surgical intervention where indicated, and

(b) The measures stated in (a), together with standard orthoptic diagnostic and training measures at times and for such periods as are indicated in the case.

To obtain data by electromyography on the effects of ocular muscle anomalies on reciprocal innervation, muscle tonus and other characteristics of muscle action.

To evaluate the usefulness of electroretinography in diagnosis of amblyopia of disuse and anomalous retinal correspondence.

To determine the usefulness of a commercial "screening device," the Orthorator in diagnostic evaluation of strabismus patients, both children and adults.

Methods employed: Patients with ocular muscle anomalies will be divided into two groups by a method of chance selection. One group will be managed by an old conventional method involving cycloplegic correction of refractive errors, occlusion of the dominant eye, and

surgical intervention where any of these measures are indicated. The other group will have, in addition, the use of various standard orthoptic measures whenever and for periods considered to be indicated.

Selected patients will be subjected to extraocular muscle electromyography to determine any variations from normal recordings.

Others with amblyopia of disuse or anomalous retinal correspondence will be tested by electroretinographic techniques for variations from normal tracings.

The Bausch and Lomb Orthorator will be used to check all strabismus patients able to cooperate with such diagnostic testing. Rechecks will be made during and after significant treatment of the muscular anomaly to indicate the usefulness of this instrument in diagnosis and follow-up of strabismus cases.

Patient Material: Both childhood and adult patients with anomalies of the extraocular muscles will be accepted by physician referral. Part of the cases will be obtained from a collaborative strabismus clinic now established at Freedmen's Hospital of Howard University.

Major Findings in 1954: No significant findings have been made. We have set up a collaborative clinic as mentioned, employed an orthoptic technician, and done a large portion of the preliminary organizational work. A few patients have been accepted and are under management.

Significance to the Institute Program: Strabismus or "crossed eyes" is due to a variety of causes. Once the anomaly has become established with reinforcement of abnormal reflex patterns it becomes difficult to restore the eyes to their normal position and at the same time achieve normal development of binocular vision. Correction of abnormal deviation of the visual axes may be achieved by surgery, but this technique does not assure a functional result in terms of normal binocular vision. We may judge that this is so because the fundamental difficulty underlying strabismus lies in the nervous control of the eye muscles and since it is impossible to operate on reflexes it becomes necessary to perform our mechanical procedures on the muscles. It is thus apparent that the surgical treatment of strabismus can accomplish no more than the restoration of normal alignment of the visual axes, which places the eyes in a favorable position for normal reflexes to develop if they are going to do so. Surgical intervention is but an incident in the long-term treatment of strabismus. Attention must be paid to encouraging the development of normal reflex patterns before and after the surgical procedure in order to achieve more than a cosmetic re-alignment of the visual axes.

More should be known of the mechanism of strabismus. Such relatively new techniques as electromyography and electroretinography should be employed to see if they can add more to this fund of knowledge.

The value of screening devices which now include chiefly the Bausch and Lomb Orthorator, the American Optical Company Sight Screener, and the Keystone View Company Telebinocular needs further investigation. These instruments may be found to have value in the ophthalmologist's office as a time saver, or in schools for strabismus case-finding.

Proposed Course: As planned.

R.P.C.-4
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-51 (C)
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$17,500	4	1	5	1.5	0.4	1.9	
FY 1956	$18,600	4	1	5	1.5	0.4	1.9	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICIAN ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

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R.P.C.-5
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-51 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases & Blindness — INSTITUTE
2. Ophthalmology Branch — LABORATORY OR BRANCH

3. _____ — SECTION
4. _____ — LOCATION (IF OTHER THAN BETHESDA)
5. NINDB-52(C) — SERIAL NO.

6. Detection of Ocular Tumor by Isotope Methods. — PROJECT TITLE

7. James F. O'Rourke, M. D. — PRINCIPAL INVESTIGATOR(S)

8. Frederick W. Sperling, Ph.D. (NIAMD) — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives. Tumors of the globe, adnexa and orbit command attention as the processes of this region most likely to endanger life. The high malignancy and rate of recurrence of many tumor types demonstrates the need for early diagnosis. It is our purpose in this project to evaluate some of the currently available isotope detection methods as they apply to the field of ocular tumors.

Methods Employed. Two isotope study methods are contemplated.

1. The in vivo study of tumor patients will take the form of direct scintillation counting with a suitable ocular counting probe (Anton #225), using adequate exposures 24 hours following the intravenous injection of P-32.

2. Electron track autoradiography of biopsied tissue specimen to demonstrate any increased isotope uptake by microphotographic techniques is to be undertaken. This will follow methods developed by Frederick Sperling, Ph.D., who will collaborate in this segment. It is anticipated that biopsy material plus aspiration of subretinal fluid will provide suitable tissue for this aspect of the project.

NINDB-52 (C)
SERIAL NO.

Patient Material. Patients in the following categories apt to conceal or simulate a malignancy are to be screened as out-patients:

1. Retinal detachment, solid or serous, without tear.
2. Unilateral exophthalmos without endocrine history.
3. Progressive and non-responsive lesions of lids and lacrimal apparatus.
4. Cysts and tumors of the iris.
5. Blind pthisical eyes, etiology unknown.
6. Infants suspected of retinoblastoma.

Major Findings. New project as of November, 1954.

Significance to Program of Institute. Such a study will permit the Ophthalmology Branch to make its contribution toward the diagnosis and treatment of malignant diseases within its area of study and to evaluate methods employed elsewhere to this end.

Proposed Course of Project. It is anticipated that acceptance of patients for screening will begin within four months. Collaboration with Dr. Sperling of NIAMD has been arranged. It is anticipated that such pathological specimens resulting from biopsy or enucleation procedures may provide material for extension of ocular pathology studies in the Ophthalmology Branch which are at present non-existent.

R.F.C. - 3
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-52 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$7,400	1	1	2	0.4	0.4	0.8	
FY 1956	$8,000	1	1	2	0.4	0.4	0.8	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

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R.P.C. - 4
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-52 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases & Blindness — INSTITUTE
2. Ophthalmology Branch — LABORATORY OR BRANCH
3. _____ — SECTION
4. _____ — LOCATION (IF OTHER THAN BETHESDA)
5. NINDB-53(C) — SERIAL NO

6. The Influence of Nutritional and Protein Factors on Prognosis in Keratoplasty — PROJECT TITLE

7. James F. O'Rourke, M. D. — PRINCIPAL INVESTIGATOR(S)

8. _____ — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives. This project, designed for activation in the latter half of 1955, will undertake a pilot study of the problems inferred in the title above, until such time as indicated expansion. The many queries addressed to the Ophthalmology Branch of the Institute (NINDB) on the subject of corneal opacities have in part motivated the decision to accept a few such patients for study in the hope that the feasibility of a more ambitious program may be gauged. It will be the general aim of this study to improve all aspects of protein balance and nutrition before and after corneal surgery. The recent work of Dr. Stocker at Duke University has served to re-emphasize the role of the endothelial cell layer in the causation of many opacity types, and further, the importance of endothelial integrity in donor and recipient eyes, if surgery is to succeed. It is reasonable to assume that nutritional factors may serve a major function in maintaining this single cell layer intact. There can be no doubt that attention to subclinical nutritional and vitamin deficiencies must be more thorough than would obtain in surgery in other body areas. The study is undertaken to improve the prognosis following surgery on certain opacity types.

Methods Employed. 1. Patients to be screened for suitability by questionnaire to referring physicians and by out-patient visits.

2. Nutritional studies for subclinical deficiencies of blood factors, detectable vitamin levels when available, liver function and corneal healing power.

3. Repeated slit lamp examinations to determine status of endothelial cell layer.

4. Admission of suitable patients for preoperative build-up with special attention to factors in number 2.

5. Donor material to be sought from district area service hospitals from donor eyes less than 40 years of age, whenever possible.

Patient Material. Sample patients will initially be drawn from a group of endothelial dystrophies and Gruenow's familial dystrophy types.

Major Findings. New project.

Significance to Program of Institute. Assistance of collaborating and consulting Institutes make possible the detection of subclinical deficiencies to degree not seen in most other areas. As mentioned, the frequent inquiries in relation to corneal disease seem to indicate the need for such a pilot study. We may then determine the advisability of accepting patients with corneal disease not admitted for treatment elsewhere because of poor prognosis or previous poor operative results.

Proposed Course of Project. Should the initial trial indicate need for expansion, such will be done within limits of professional staff.

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-53 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$7,400	1	1	2	0.4	0.4	0.8	
FY 1956	$8,000	1	1	2	0.4	0.4	0.8	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

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R.P.C. - 4
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-53 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C.-1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness 2. Ophthalmology
INSTITUTE LABORATORY OR BRANCH

3. _____ 4. _____ 5. NINDB 54 (C)
SECTION LOCATION (IF OTHER THAN BETHESDA) SERIAL NO.

6. Evaluation of Newer Steroids in the Treatment of Experimental and Clinical Uveitis.
PROJECT TITLE

7. James F. O'Rourke, M.D.
PRINCIPAL INVESTIGATOR

8. Ralph W. Ryan, M.D., and Gilbert Iser, M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: Newer steroid principles at present under investigation in N.I.A.M.D. have not as yet been evaluated in regard to their effects on ocular inflammation. A comparison of the effects of the most promising of this new group (metacortin) with presently available steroids (cortisone and hydrocortisone) is desirable, therefore. It will be our purpose to demonstrate the presence or absence of increased therapeutic effects of this newer principle both in the treatment of experimental uveitis and on selected clinical patients.

Methods Employed: 1. Induction of a reproducible granulomatous type uveitis by the intravitreal injection of horse serum in previously sensitized rabbits. 2. Estimation of the relative blocking effect of the three steroids by the institution of treatments 48 hours prior to shock dose injection into all eyes. Grading of lesions to be based on severity and duration of chemosis, precipitates and aqueous flare in treated and control animals. 3. Repetition of lesion induction above on a series of rabbits with treatment by intramuscular injections to continue one week longer. Enucleation of animals from each group plus control group on the 3rd, 5th, 7th and 10th day. Histopathologic studies for differences in degree of cellular response will be made.

Patient Material: Clinical trials of the new steroid principle metacortin will be at first limited to topical application in patients with anterior nongranulomatous uveitis. Such patients will

be screened as out-patients for suitability and those selected will be given a 48 to 72 hour trial of the newer drug. Should no response follow, treatment will revert to standard methods with older steroids plus routine uveitis care. Drs. Ralph W. Ryan and Gilbert Iser will conduct this segment of the project. Basic uveitis work-up will include those studies that obtained in the toxoplasmosis project recently reported. Essentially, these include X-ray, blood studies and skin tests.

Major findings: The only previous trials with metacortin have occurred in N.I.A.M.D. in the treatment of rheumatoid arthritis. It is reported that increased therapeutic effects with fewer undesirable side effects permit the opinion that the drug shows promise. No previous studies on ocular inflammation are recorded.

Significance to Institute Program: Collaboration with Dr. Maurice Pechet of N.I.A.M.D. will permit evaluation of the steroid effects on ocular tissue inflammation and thus help to complete the evaluation of its effect on hypersensitivity response in general.

Proposed Course: Should the drug show promise, further studies of its ocular penetrability are contemplated. Initial arrangements for this estimation have been completed.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-54 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$17,500	3	2	5	1.1	0.8	1.9	
FY 1956	$18,600	3	2	5	1.1	0.8	1.9	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

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R.P.C. - 4
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-54 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C. 1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Ophthalmology — LABORATORY OR BRANCH
3. _____ — SECTION
4. _____ — LOCATION (IF OTHER THAN BETHESDA)
5. NINDB 55 (C) — SERIAL NO.

6. Transmission and Scattering of Light by the Cornea
PROJECT TITLE

7. William M. Hart, M.D.
PRINCIPAL INVESTIGATOR(S)

8. Ralph D. Gunkel, M.S. (Physics)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To study effects on transmission and scattering of light by corneal tissue associated with varying conditions of pH, hydration, electrolyte balance, molecular aggregation and physical stress.

To conduct similar studies on corneas with opacities.

Methods employed: A specially adapted "light scattering" microphotometer will be used to measure the transmitted component and determine the scattering of rays from a beam of light directed through the corneal tissue. The corneal tissue will then be subjected to the varying conditions mentioned under objectives and similar measurements recorded on light scattering.

Patient Material: Most of the studies will be carried out on animal corneas, but human corneas obtained from surgical enucleation or from autopsies will be examined.

Major Findings in 1954: Facilities were not complete.

Significance to Institute Program: The cornea and sclera of the eye are both composed of collagenous fibers. The cornea is transparent and must remain so in order for the visual process to function,

while the sclera is opaque and white in color. The reason for this optical difference has been the subject of much investigation because opacities of the cornea are an important cause of blindness and in the past there has been no treatment for this condition except surgical transplantation of normal tissue. The physical factors affecting the transmission of light by the cornea and sclera have been under investigation. There are generally two schools of thought accounting for the peculiar optical properties of the cornea. According to one of these the cornea is able to maintain its transparency because its limiting membranes are semi-permeable in nature and thus act to keep down the water content of the cornea. Following damage to these membranes the cornea swells and some degree of opacity results. The second school of thought points to the numerous physical factors which are known to affect the transmission of light by any colloid system. A prominent feature of this physical structure is the orderly arrangement of fibers in the cornea which gives rise to a birefringent system. Opacity of the cornea may result from any mechanical disarrangement of fibers in the cornea or from alteration of a number of environmental chemical factors beyond physiological limits. Since it has been shown that hydration does not materially affect the transmission of light by other colloid systems, it is unlikely that this mechanism is unique in the cornea.

Proposed Course of Project: To be carried out when facilities permit.

R.P.C. 3
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-55 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$10,200	2	1	3	0.7	0.4	1.1	
FY 1956	$11,000	2	1	3	0.7	0.4	1.1	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICIAN ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

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R.P.C. 4
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-55 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C.-1
Dec. 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness (INSTITUTE) 2. Ophthalmology (LABORATORY OR BRANCH)

3. _____ (SECTION) 4. _____ (LOCATION (IF OTHER THAN BETHESDA)) 5. NINDB-56(C) (SERIAL NO.)

6. Improvement in the Design and Construction of Ophthalmic Instruments
PROJECT TITLE

7. Ralph D. Gunkel, M.S., O.D.
PRINCIPAL INVESTIGATOR(S)

8. Ralph W. Ryan, M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To make improvements in the instruments used in ophthalmic examination or treatment.

Specifically: To design and construct a self-recording tangent screen, using magnetic test objects and to be operated without a wand or other distracting influence on the patient.

To design and construct a hemispherical perimeter which is self-recording, operates with magnetic test objects without use of a wand, and fulfills the purposes of both a perimeter and a tangent screen. This must be inexpensive enough to be used by practicing Ophthalmologists.

To adapt a non-varying, non-flickering light source to the Bausch and Lomb retinal camera for greater uniformity in pictures than is now possible with the carbon arc light.

Methods employed: The application of logic and inventive genius to solve the problems of improved design for greater accuracy, efficiency and reduction of effort for both the examiner and patient is the aim of this project. The instruments to be improved are ones whose present form leave much to be desired. The instruments will be constructed along the desired lines and tested in our own clinics until a model is deemed worthy of presentation at the annual meeting of the American Academy of Ophthalmology. Efforts will be made to evaluate cost of quantity production of the instruments and facilitate their introduction to Ophthalmologists.

Major findings in 1954: A good working model of a greatly improved tangent screen has been in use for over 6 months and has been well-tested in our Clinics. It has all the features we desired and cuts time required for charting a field to about one-half that required for the conventional tangent screen with hand activated test objects and pins. Permission has been requested to present it at the meeting of the American Academy of Ophthalmology in October, 1955.

Significance to Instrument Program: The improvement of instruments to save Ophthalmologists time and increase the accuracy and efficiency of examination of patients will well justify the expense incurred in developing them.

Proposed course of Project: To be continued as planned.

R.P.C.- 3
Dec. 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-56 (C)
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$10,200	2	1	3	0.7	0.4	1.1	
FY 1956	$11,000	2	1	3	0.7	0.4	1.1	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICIAN ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

R.P.C. - 4
Dec. 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-56 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Electroencephalography
LABORATORY OR BRANCH

3. _____
SECTION

4. _____
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-57(C)
SERIAL NO.

6. Electrographic (EEG and ECoG) study of temporal lobe epilepsy
PROJECT TITLE

7. C. Ajmone Marsan
PRINCIPAL INVESTIGATOR

8. Maitland Baldwin
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The two main objectives of this project are: a) to gain more information on the physiopathology underlying this particular form of epilepsy; b) to establish reliable criteria in the electroencephalographic diagnosis of this disorder. In considering the surgical treatment of this form of epilepsy, the selection of patients becomes of paramount importance and the EEG findings are almost always those upon which this selection is based. In recent years considerable material has been accumulated in this field, yet we are still unable to answer a number of important questions, among which:

a) is the epileptogenic lesion cortical (i.e., susceptible to surgery) or subcortical (i.e., non-operable)? What are the EEG criteria to differentiate the two forms?

b) Why some forms of temporal abnormalities can be activated during sleep while others are unaffected or decreased?

c) Why apparently similar clinical seizures have rather different electrographic correlates?

d) What are the relations between parasagittal region and temporal lobe?

Methods employed and patient material: This main project is, therefore, subdivided into the following sub-sections:

A) EEG diagnosis of temporal lobe epilepsy.
B) Electrocorticographic study of temporal lobe discharges.
C) Electrographic-clinical correlations of epileptic seizures.
D) Sleep and temporal lobe epilepsy.
E) Electrographic manifestations of sub-cortical epileptogenic lesion.
F) Clinical-pathological correlations in cases with parasagittal and temporal EEG abnormalities.
G) Cortical physiology in man (electrocorticographic study of spontaneous, evoked, and abnormal activity with particular emphasis on the temporal region).

Routine EEG examinations are carried out on all epileptic patients admitted by the Neurosurgical Branch. Numerous tracings are obtained in various conditions (after withdrawal of medication, during induced sleep, during spontaneous or induced seizures) using a minimum of 21 electrodes and various methods of localization. If the patient is eventually selected for surgical treatment, the electrical activity will be recorded from its exposed cortex both at rest and following electrical stimulation of various cortical and subcortical structures, before and after surgical ablation of the abnormal tissue. EEGs are then taken at regular intervals in the post-operative period.

Major findings: This is a long range project in which positive and useful results can only be obtained with a large number of cases and with pathological and clinical correlations. The clinical evaluation of surgical treatment of epilepsy requires a minimum of one to three years follow-up and most of the conclusions in regard to electroencephalographic criteria for physiopathology and diagnosis will obviously depend upon the surgical results. This limitation applies particularly to the sub-sections A, D, E, F, and partly to sub-sections B and C. Interesting observations were however made (sub-sections B and G) on the electrical activity of the exposed insula where epileptiform discharges can often be recorded. The behavior of paroxysmal abnormalities following cortical undercutting, and their relation with electrically induced afterdischarge was also investigated. The effect of arousal, acoustic stimulation and speech upon the spontaneous activity of various regions of the temporal cortex was studied.

Significance to the program of the Institute: The main program of the Neurosurgical Branch of the NINDB concerns the temporal lobe epilepsy. This particular research project of our Branch is a primary adjunct to the research of the Neurosurgical Branch.

Proposed course of project: Fundamentally unchanged.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-57 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$7,000	2	3	5	0.5	0.7	1.2	
FY 1956	$7,725	2	3	5	0.5	0.7	1.2	

12. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

Branch of Neurological Surgery - NINDB
Section of Neuropathology - NINDB

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-57 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Electroencephalography — LABORATORY OR BRANCH
3. _____ — SECTION
4. _____ — LOCATION (IF OTHER THAN BETHESDA)
5. NINDB-58 (C) — SERIAL NO.

6. Thalamo-cortical relationship — PROJECT TITLE

7. C. Ajmone Marsan — PRINCIPAL INVESTIGATOR

8. _____ — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The main interest of this study concerns the mechanism of the "recruiting response" which can be evoked on different cortical regions following stimulation of non-specific thalamic nuclei. The anatomical and physiological evidence provided in the last years is not sufficient to explain many of the features of this peculiar type of response; the pathway from the various thalamic nuclei to each cortical region are still under discussion; no satisfactory explanation has been offered to account for the variations in latency and amplitude of the response itself; the significance of the subcortical connections of the non-specific thalamic system is poorly understood.

Methods employed: The experiments are carried out on cat under nembutal anesthesia. Electrical stimulation of subcortical structures is performed by means of steel electrodes inserted and held in place by a stereotaxic instrument. The square pulses of various duration, voltage and frequency are obtained from two Grass stimulators in order to evaluate the inter-relation between two different structures stimulated at variable delay. Cortical and subcortical recordings are made with oscilloscopic and ink-writing techniques with standard apparatuses (Dumont CRO; Offner EEG; Grass pre-amplif.)

Major findings: The lack of histological control to confirm the position of stimulating and recording electrodes prevents for the present moment, any definite conclusion. It seems, however, that:
a) the non-specific thalamic system does not behave as a whole but each nucleus or at least parts of the system itself behave differently, both from an anatomical and physiological standpoint.
b) the latency of the cortical response varies not only from nucleus to nucleus but in the case of the same nucleus as well; in this last case, the variation shows a definite, regular pattern, clearly related to the waxing and waning phases of the recruiting response.
c) The necessity of an optimal or critical frequency of stimulation is confirmed; however, this frequency varies rather widely from nucleus to nucleus; single pulses can, at times evoke a cortical response which has completely different characteristics, although the stimulated spot is the same.
d) The basal ganglia do show a recruiting response similar to that obtainable on the cortex but there is no physiological evidence to suggest that any part of this basal complex is an important link in the thalamo-cortical pathway.

Significance to the program of the Institute: The system under investigation seems to be involved in certain types of epileptic disorders. A deeper knowledge of its physiology could probably throw some light on the complex mechanisms underlying psychoparetic manifestations, alterations of awareness and attention commonly found in epileptics.

Proposed course of project: a) detailed study of parameters of stimulation for the recruiting response; b) inter-relationship between association nuclei of the thalamus and non-specific system; c) inter-relationship between cortico-cortical responses and non-specific thalamic responses; d) effect of convulsant drugs upon non-specific system; e) cortical and non-cortical components of the non-specific response; f) relations between limbic system and non-specific thalamic system.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-58 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$7,000	1	3	4	0.5	0.8	1.3	
FY 1956	$7,725	1	3	4	0.5	0.8	1.3	

12. BUDGET ACTIVITY:

RESEARCH [x] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-58 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Electroencephalography
LABORATORY OR BRANCH

3. _____
SECTION

4. _____
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-52 (C)
SERIAL NO.

6. Electroencephalographic control of anti-convulsant therapy
PROJECT TITLE

7. C. Ajmone Marsan and D. Tower
PRINCIPAL INVESTIGATORS

8. _____
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

See Serial No. NINDB-16(C).

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-59 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1955	$7,000	2	3	5	0.5	0.7	1.2	
FY 1956	$7,725	2	3	5	0.5	0.7	1.2	

12. BUDGET ACTIVITY:

RESEARCH [x] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I).

Section of Neurochemistry NINDB

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

See Serial No. NINDB-16(C)

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-59 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

See Serial No. NINDB-16(C)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Electroencephalography
LABORATORY OR BRANCH

3. _____
SECTION

4. _____
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-60 (C)
SERIAL NO.

6. Electrographic study in cases of cerebral palsy with seizures
PROJECT TITLE

7. C. Ajmone Marsan
PRINCIPAL INVESTIGATOR

8. Maitland Baldwin
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To establish diagnostic and prognostic criteria in regard to the outcome of seizures in case of massive cerebral lesions when medical treatment has failed and the patient is a possible candidate for surgery.

Methods employed and patient material: Serial EEG examinations are carried out on patients admitted by the branch of Neurological surgery. The electrographic study is performed in different conditions and with various activating procedures. Particular emphasis is placed on localizing devices and in differentiating cortical from sub-cortical lesions. In cases of surgical operation, the exposure of an entire hemisphere provides unparalleled opportunities for electrical exploration of various cortical areas and of a number of subcortical structures.

Major findings: A limited number of patients have been studied in this relatively recent project. A long clinical and electrographic follow-up are needed in order to assess the validity of any offered interpretation.

Significance to the program of the Institute: This project is an important complement to similar researches for the coming year in the

section of Neuropathology and in the Branch of Neurological Surgery of the NINDB.

Proposed course of the project: Accumulate wider information through a larger number of patients with a longer post-operative follow-up. At least 2-3 years project period.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-60 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGET POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$6,900	2	3	5	0.5	0.8	1.3	
FY 1956	$7,725	2	3	5	0.5	0.8	1.3	

12. BUDGET ACTIVITY:

RESEARCH [x] ADMINISTRATION

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THE PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM L)

Branch of Neurological Surgery NINDB
Section of Neuropathology NINDB

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, (OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-60 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

None.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

None.

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases & Blindness — INSTITUTE
2. Epidemiology Branch — LABORATORY OR BRANCH

3. _____ — SECTION
4. Rochester, Minnesota — LOCATION(IF OTHER THAN BETHESDA
5. NINDB-61 (C) — SERIAL NO.

6. Epidemiologic Survey of Selected Chronic Neurologic and Neuro-Ophthalmologic Disorders in the United States and Canada: 1. Rochester, Minnesota (Pilot Study)
PROJECT TITLE

7. Leonard T. Kurland, M.D., Dr. P.H.
PRINCIPAL INVESTIGATOR

8. Joseph Berkson, M.D., Division of Biometry and Medical Statics, Mayo Clinic
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

OBJECTIVE AND METHODS:

This is the first (and "pilot" study) in our effort to determine the frequency, geographic distribution, and population selectivity in the United States and Canada for a large number of neurologic and neuro-ophthalmologic disorders of unknown etiology. The collection and analysis of such data are considered basic to the epidemiologic approach; such information has been utilized in previous investigations of multiple sclerosis and amyotrophic lateral sclerosis.

The town of Rochester, Minnesota has a population of about 30,000. It is believed that almost all persons in the community with neurologic or neuro-ophthalmologic disorders requiring medical care will be examined at the Mayo Clinic. The record system at this institution is believed to be one of the finest for statistical research.

All records for the previous ten years of residents of Rochester, in which a diagnosis has been made of one of the neurologic,

neuromuscular, or neuro-ophthalmologic disorders under consideration are reviewed and abstracted. Data on each disorder are then analyzed statistically.

The aims of the study are: (1) to determine the feasibility of such an approach for numerous disorders for which no frequency data are available; (2) to determine which type of statistical information is available by such record analysis; and (3) to estimate the annual incidence and the prevalence in the larger communities to be studied later. The latter information is based on the small but intensively studied sample in Rochester combined with the extensive (but less accurate) data available in the national mortality records of the United States and Canada.

MAJOR FINDINGS:

The selection of Rochester, Minnesota, for this pilot study seems to have been a satisfactory choice. The analysis of the data in Rochester is now under way.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE

There are few reliable statistics on the frequency and distribution of most of the neurologic disorders a d myopathies. Such information is basic to future epidemiologic studies which would be expected to supply useful baseline data for comparative studies and useful leads for future laboratory and clinical research.

PROPOSED COURSE OF PROJECT:

This pilot study of Rochester, Minnesota neurologic cases is to be followed by another study of a small medical center, perhaps Burlington (Vt.), before undertaking the first of the major surveys in the five to eight larger medical centers in the United States and Canada. The analysis of mortality statistics in the United States and Canada is expected to begin in 1955.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-61 (C)
SERIAL NO.

11.
BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL
FY 1955	$4,945	1	1	2	½	½	1
FY 1956	$5,790	2	2	4	1	1	2

12.
BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13.
IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

Mayo Clinic, Rochester, Minnesota

14.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

R.P.C. - 3
December 1954

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-61 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Kurland, L.T. and Westlund, K.B. Epidemiologic factors in the etiology and prognosis of multiple sclerosis. Annals of the New York Academy of Sciences, 58: 682-701, July 28, 1954.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness — INSTITUTE
2. Epidemiology Branch — LABORATORY OR BRANCH
3. _____ — SECTION
4. Rochester, Minnesota — LOCATION(OTHER THAN BETHESDA
5. NINDB-62 (C) — SERIAL NO.

6. Investigation of Amyotrophic Lateral Sclerosis: Epidemiologic, Genetic, Clinical, Pathologic, and Therapeutic Studies — PROJECT TITLE

7. Leonard T. Kurland, M.D., Dr. P.H. — PRINCIPAL INVESTIGATOR

Clinical and Therapeutic--Donald W. Mulder, M.D., Consultant in Neurology, Mayo Clinic
Chamorro Studies: Lorenzo, L.G. Iriarte, Medical Assistant, Guam Memorial Hospital
Obstetrics: Wilson Houston, Cdr. (MC) USN, Chief of Obstetrics, U.S. Naval Hospital, Guam
Pathological Anatomy: George Sayre, M.D., Section of Pathology, Mayo Clinic
Clinical Pathology on Guam: Michele Gerundo, M.D., Chief of the Laboratory, Guam Memorial Hospital
Electromyography: Edward Lambert, M.D., Electromyographer, Mayo Clinic
Gastric Cytology Mayo Clinic: J.R. McDonald, M.D,, Department of Surgical Pathology, Mayo Clinic and Cyrus E. Rubin, M.D., Department of Medicine, University of Washington, Seattle
Nutritional Studies: Marjorie Grant Whiting, Department of Nutrition, Harvard School of Public Health

8. _____ — OTHER INVESTIGATOR(S)

9. PROJECT DESCRIPTION

OBJECTIVES:

To review and clarify aspects of motor neurone disease (amyotrophic lateral sclerosis and its clinical components - progressive muscular atrophy and progressive bulbar palsy) and determine the reason for the unusual prevalence in the Mariana Islands.

METHODS EMPLOYED:

An unusual opportunity to investigate the problem is afforded by the extremely high prevalence of A.L.S. among the Chamorros (natives) of Guam and the other Mariana Islands in the Western Pacific. Unusual or suspicious findings are studied further and more elaborately with patients from other sources, particularly the Mayo Clinic.

1. Clinical description of patients on Guam and at the Mayo Clinic with an analysis of the principal clinical features is under way. In addition to numerous "by-product" investigations described below, the effect of pregnancy on A.L.S. and A.L.S. on pregnancy has been reviewed.

2. Clinical Pathology: Various blood and spinal fluid biochemical and genetic typing (blood groups) are being conducted at the Guam Memorial Hospital (Dr. Gerundo)to determine if any variation from the normal can be noted. Unusual findings recorded by Dr. Gerundo are then checked with results of similar tests on Mayo Clinic patients.

At the Mayo Clinic an investigation to determine if any abnormality in gastric cytology by chymotrypsin lavage method is at present under way. (Drs. McDonald and Rubin)

Electromyographic studies of patients on Guam by Dr. Ed Lambert are now in progress; an attempt to determine if EMG is of predictive value among siblings of patients is being carried out.

3. Pathological Anatomy: Material collected in Guam and from Mayo Clinic patients is being examined. (Dr. Sayre) Particular interest in the latter group is centered on those patients with a positive family history of motor neurone disease.

4. Epidemiology and Genetics; Statistical data have been col- from mortality reports in the United States, Canada, and several European and Asiatic countries. Morbidity data from Rochester, Minnesota were also obtained. The prevalence rates among the Chamorros and other population groups in the Marianas and surrounding island groups were studied. Population selectivity factors in these islands were evaluated. An attempt was made to determine the duration of the disease among the Chamorros and the source of the disease among the people. Factors responsible for the observed familial aggregation of cases were investigated. Comparisons of familial incidence among patients and a random sample "control" group are being determined. In these latter groups a comparison of possible etiologic agents is being investigated.

5. Therapeutic Studies: Among the large group of patients on Guam and among selected patients at the Mayo Clinic and those obtained through the Clinical Center several agents are being tested.

PATIENT MATERIAL:

As explained above, patients with motor neurone disease on Guam, at the Mayo Clinic, and those obtained through the Clinical Center are included in this investigation. At any one time in Guam there are, among the 30,000 population, over 125 affected individuals; and at the Mayo Clinic, approximately 150 new patients are seen each year. Patients are selected from these groups.

MAJOR FINDINGS DURING THE CALENDAR YEAR:

Clinically and pathologically, the A.I.S. observed on Guam is the same as that observed elsewhere. It is at least 100 times as prevalent among the Chamorros as among any other population group studied. It is highly selective for the Chamorro people only and is not found among other populations living in the Mariana Islands. The familial aggregation appears to be unusually high among the families studied on Guam. To date no obvious external etiologic agent has been noted. Amyotrophic lateral slcerosis has been prevalent over 100 years on Guam and may have been introduced about the time of the conquest of the island by Spain in 1700.

No unusual clinical laboratory observations have as yet been observec among the patient group on Guam. Pathological material obtained from patients on Guam or from cases of familial A.L.S. observed in the continental U.S. does not appear to be different from the apparent "sporadic" form seen worldwide.

Ideally, studies of pedigrees of patients on Guam would indicate whether a genetic factor is of prime importance. The destruction of written records by the elements and by war, a high rate of illiteracy among older Guamanians, and the fairly high rate of illegitimacy in the native population have made it difficult to obtain accurate family information.

Although the fact that a number of potentially toxic food agents are ingested by the poorer native population, no apparent difference in the use of such materials has been found among controls and the patient population under study. The same may be said for exposure to various forms of stress or trauma and recognized infectious agents. A.I.S. not affected by pregnancy and v.v.

SIGNIFICANCE OF THE PROGRAM TO NIH:

In addition to providing clinical data for an important disease of the nervous system, the study illustrates the value of the combined field of epidemiologic and clinical approach.

Clarification of the etiology of the disorder would be expected to improve the opportunity for therapeutic success.

PROPOSED COURSE OF PROJECT:

All the above projects are still under way. Expansion of the Clinical, laboratory, and genetic determinations is contemplated.

In addition, a study to determine the relative importance of external and genetic factors in explaining the high prevalence of A.L.S. among the Guamanians is scheduled to begin this summer among a large group of Guamanial families living in California.

R.P.C. - 2
December 1954

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-62 (C)
SERIAL NO.

11.
BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL
FY 1955	$4,945	1	1	2	½	½	1
FY 1956	$5,790	2	2	4	1	1	2

12.
BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE

13.
IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956; IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

U.S. Navy: Bureau of Medicine and Surgery, U.S. Naval Hospital on Guam
Goverment of Guam: Department of Medical Services
Mayo Clinic

14.
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS,) IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

NONE

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-62 (C)

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1954:

Kurland, L.T. and Mulder, D.W., Epidemiologic Investigations of Amyotrophic Lateral Sclerosis. 1. Preliminary Report on Geographic Distribution, with Special Reference to the Mariana Islands, Including Clinical and Pathologic Observations. Neurology, 4(Nos. 5-6): 355-378; 438-448, May-June, 1954.

Mulder, D.W., Kurland, L.T., Iriarte, LL.G., Neurologic Diseases on the Island of Guam. U.S. Armed Forces Medical Journal, V (No.12): 1724-1739, December, 1954.

Mulder, D.W. and Kurland, L.T. Amyotrophic Lateral Sclerosis in Micronesia. Proceedings of the Staff of the Mayo Clinic, 29 (No.26): 666-670, December 22, 1954.

Kurland, L.T. and Mulder, D.W.: Epidemiologic Investigations of Amyotrophic Lateral Sclerosis. 2. Familial Aggregations Indicative of Dominant Inheritance. Neurology (To be published in March and April, 1955)

Kurland, L.T., Mulder, D.W., and Westlund, K.B., Multiple Sclerosis and Amyotrophic Lateral Sclerosis: Etiologic Significance of Recent Epidemiologic and Genetic Studies. New England Journal of Medicine (To be published during 1955.)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1954:

NONE

R.P.C. - 1
December 1954

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Cerebral Palsy Project
LABORATORY OR BRANCH

3. Medical Neurology
SECTION

4. _____
LOCATION

5. NINDB-63(C)
SERIAL NO.

6. Clinicopathologic analysis of cerebral palsy.

7. Pearce Bailey, M. D.
PROGRAM DIRECTOR

Henry A. Imus, Ph.D.
PROJECT DIRECTOR

8. G. Milton Shy, M.D., Maitland Baldwin, M.D., Anatole S. Dekaban, M.D., Ellsworth C. Alvord, M.D., William F. Windle, Ph.D., and J.G. Greenfield, M.D.
INVESTIGATORS

9. PROJECT DESCRIPTION

Project: Correlation of clinical and pathologic findings in a large number of cases of cerebral palsy.

Objectives: To provide clues to the etiology of the various forms of cerebral palsy which can be obtained only by a large, collaborative approach to the study of this complex disease.

Methods Employed: In cases of cerebral palsy detailed reports are obtained of prenatal history, birth and neonatal progress, clinical history and findings from birth until death, cause and method of death and full autopsy protocol. The brain and spinal cord are removed, fixed, and sectioned for clinicopathologic analyses.

R.P.C. - 1(a)
December 1954

Patient material: (1954 calendar year)

		No.	Average Stay Days
Admissions:	Adult males	4	196
	Adult females	2	310
	Children	2	49

Major findings: New project, no results to date.

Significance to NEUROLOGY Research: It is generally recognized that no broad research attack can be made on the problem of cerebral palsy in infants and children until a systematic analysis is made of the clinical and pathological correlates of the variety of conditions which are manifest in cerebral palsy. Precise classification is an essential prerequisite to comprehensive etiological studies. Determination of the etiology in turn is prerequisite to prevention and treatment of disease.

Proposed course of project: This is a long term, longitudinal study of cases of cerebral palsy requiring a significantly large number of cases. In addition to those cases obtained from local hospitals, it is anticipated that a number of other hospitals and institutions will provide additional material through the Research Grants Program. This collaborative effort is essential because an adequate number of cases could not be obtained in any other way.

In addition, a study now underway on physiological and anatomical mechanisms which form the substrata of choreoathetosis, a form of cerebral palsy in which uncontrollable and incapacitating abnormal movements predominate, will be incorporated. An attempt will be made to develop surgical procedures for symptomatic relief for such cases.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-63(C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1955	$ 68,000	6	5	11	4	3.7	7.7	555
FY 1956	$100,000	7	5	12	7	5	12	1665

12. BUDGET ACTIVITY:

RESEARCH [x] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] TECHNICAL ASSISTANCE [ ]

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

NINDB-L-9. A study with animals on the experimental production of anomalies similar to cerebral palsy by means of asphyxia at birth, drugs commonly used in obstetrical practice and other methods.

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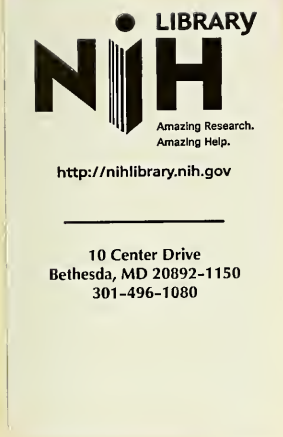
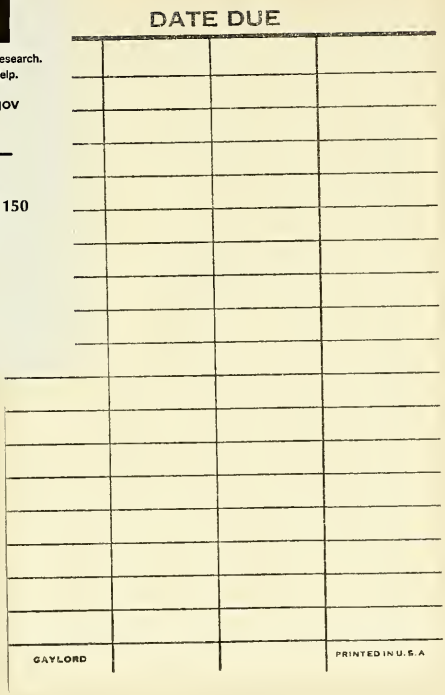
Bethesda, Maryland 20014





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